Medicaid Dossier for *Veramyst*

This information is provided in response to your request for information about Veramyst® (fluticasone furoate) Nasal Spray.

Some information contained in this response may not be included in the approved Prescribing Information. This response is not intended to offer recommendations for administering this product in a manner inconsistent with its approved labeling.

In order for GlaxoSmithKline to monitor the safety of our products, we encourage healthcare professionals to report adverse events or suspected overdoses to the company at 888-825-5249. Please consult the attached Prescribing Information.

This response was developed according to the principles of evidence-based medicine and, therefore, references may not be all-inclusive.

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Section 7.2 Comparison with Fexofenadine (March 2008) - Addition of data from 2 well-controlled studies in patients 12 years of age and older with SAR. *Veramyst* significantly improved nasal symptoms of SAR compared with fexofenadine and compared with placebo. Improvements in ocular symptoms were significantly greater with *Veramyst* compared with placebo and were comparable with improvements seen with fexofenadine.

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2. EXECUTIVE SUMMARY

DISEASE: ALLERGIC RHINITIS

- Nasal allergies are one of the most prevalent and chronic diseases in the United States, affecting up to 50 million people,[1] including 10 to 30 percent of adults and up to 40 percent of children.[2]
- Allergic rhinitis has been associated with affects on patients' quality of life including fatigue and daytime sleepiness,[3,4] daily activity impairment,[5,6] reduced work productivity,[5,6,7] impaired cognitive functioning,[8,9] reduced learning abilities,[10] impaired sleep,[11] and impaired quality of life.[4]
- Allergic rhinitis is estimated to cause 3.5 million lost workdays and >2 million missed school days per year.[12]
- For adults, seasonal allergic rhinitis (SAR) is a major cause of work absenteeism and reduced productivity, resulting in nearly $4 billion annually in lost productivity,[2] and $1,000 per day per worker in lost productivity.[13]
- Approximately 14 million physician office visits each year are attributed to allergic rhinitis.[14]
- Intranasal corticosteroids (INS) reduce the inflammation that is a root cause of nasal allergies,[15] and have been proven effective for the treatment of all 4 nasal symptoms (congestion, rhinorrhea, sneezing, and nasal itching) in both SAR and perennial allergic rhinitis (PAR).[16,17]

BENEFITS OF *VERAMYST*:

- *Veramyst* is the first and only INS proven to help relieve all 4 nasal symptoms (congestion, rhinorrhea, sneezing, and nasal itching), and all 3 ocular symptoms (itching/burning, tearing/watering, redness), assessed as a secondary endpoint, in patients 12 years and older with SAR in 5 prospectively designed and replicated studies.
- *Veramyst* is approved for use in children down to 2 years of age.
- *Veramyst* has demonstrated improvement in overall disease-specific quality of life in adult and adolescent patients with SAR.
- *Veramyst* has demonstrated significant symptom improvement within 24 hours for patients with SAR. Patients with PAR experience significant symptom improvement after day 4 of treatment. Maximum benefit may take up to several days.
- *Veramyst* has a unique ergonomically designed nasal delivery device with a side actuator that releases a consistent, low volume mist thru a small short nozzle with each actuation. It does not require daily priming and the unscented, alcohol-free, aqueous formulation can be viewed through the indicator window.
- *Veramyst* is approved for once daily administration and offers a flexible dosing option based on patients' symptom control.

EFFICACY:

- *Veramyst* 110 mcg once daily produced significant improvements in reflective total nasal symptoms scores (rTNSS), morning pre-dose instantaneous total nasal symptoms scores (AM iTNSS), and reflective total ocular symptoms scores (rTOSS) compared with vehicle-placebo in three 2-week, pivotal efficacy trials in adult and adolescent patients 12 years of age and older with SAR.[18,19,20]
- *Veramyst* 110 mcg once daily produced significant improvements in rTNSS and AM iTNSS compared with vehicle-placebo in a 4-week clinical trial[21] and a 6-week clinical trial[22] in adult and adolescent patients 12 years of age and older with PAR.
- *Veramyst* 110 mcg once daily significantly improved rTOSS, a secondary endpoint, compared with vehicle-placebo in the 6-week PAR clinical trial.[22] In the 4-week PAR clinical trial, *Veramyst* 110 mcg once daily did not demonstrate any significant improvements in ocular symptoms compared with vehicle-placebo.[23]
- *Veramyst* 110 mcg once daily for 2 weeks significantly improved nighttime symptom score (NSS) and all other secondary nasal efficacy endpoints (daytime, nighttime, 24-hour, and iTNSS) compared with fexofenadine 180 mg once daily and compared with placebo in 2 well-controlled studies in adults and adolescents 12 years of age and older with SAR. Improvements in ocular symptoms

(daytime, nighttime, 24-hour, and iTOSS) were significantly greater compared with placebo and were comparable with improvements seen with fexofenadine.[24,25]

- *Veramyst* 55 or 110 mcg once daily for 2 to 12 weeks generally produced greater improvements in rTNSS compared with vehicle-placebo in 2 pivotal efficacy trials in pediatric patients 2 to 11 years of age with SAR or PAR. rTNSS was significantly improved with the 110 mcg dose in the SAR study and with the 55 mcg dose in the PAR study.[26,27]
- *Veramyst* 110 mcg once daily produced statistically significant and clinically meaningful improvements in overall quality of life as assessed by the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) compared with vehicle-placebo in three 2-week clinical trials in adult and adolescent patients 12 years of age and older with SAR.[18,20,28]
- In adult and adolescent patients with PAR, *Veramyst* 110 mcg once daily for 6 weeks produced statistically significant and clinically meaningful improvements in overall RQLQ compared with vehicle-placebo.[29] In the 4-week clinical trial, there were no statistically significant or clinically meaningful improvements in overall RQLQ between *Veramyst* and vehicle-placebo.[23]

SAFETY:

- Overall, adverse reactions to *Veramyst* were similar to vehicle-placebo and occurred with approximately the same frequency.[23]
- In clinical trials of 2 to 6 weeks, common adverse reactions in patients 12 years of age and older treated with *Veramyst* 110 mcg versus placebo were headache (9% vs. 7%), epistaxis (6% vs. 4%), pharyngolaryngeal pain (2% vs. 1%), nasal ulceration (1% vs. <1%), and back pain (1% vs. <1%).[23] Less than 3% of patients discontinued therapy because of adverse reactions. The rate of withdrawal among patients receiving *Veramyst* was similar or lower than the rate among placebo-treated patients.
- In clinical trials of 2 to 12 weeks, common adverse reactions in patients 2 to <12 years of age treated with *Veramyst* 55 mcg, 110 mcg versus placebo were headache (8%, 8%, vs. 7%), nasopharyngitis (5%, 5%, vs. 5%), epistaxis (5%, 4%, vs. 4%), pyrexia (5%, 4%, vs. 2%), pharyngolaryngeal pain (4%, 3%, vs. 3%), and cough (3%, 4%, vs. 3%).[23] Pyrexia occurred more frequently in children 2 to <6 years of age compared with children 6 to <12 years.
- Adverse reactions reported during a long-term, 52-week clinical study of adults and adolescents with PAR were similar in type and rate between treatment groups with exception of epistaxis which occurred more frequently in patients treated with *Veramyst* (123/605, 20%) than in placebo-treated patients (17/201, 8%).[30] The epistaxis tended to be more severe in patients treated with *Veramyst*, as all 17 reports of epistaxis in the placebo-treated patients were of mild intensity, while 83, 39, and 1 of the total 123 epistaxis events in patients treated with *Veramyst* were of mild, moderate, and severe intensity, respectively. Epistaxis led to the withdrawal of 15 patients (2%) in the group receiving *Veramyst* and no subjects in the placebo group.[31] No patient experienced a nasal septal perforation during the study.[23]

INDICATION:

- *Veramyst* is indicated for the treatment of the symptoms of seasonal and perennial allergic rhinitis in patients 2 years of age and older.[23]

DOSING:

- **Adults and Adolescents 12 Years of Age and Older:** Start with 110 mcg once daily administered as 2 sprays (27.5 mcg/spray) in each nostril.[23] Titrate to the minimum effective dosage to reduce the possibility of side effects. When the maximum benefit has been achieved and symptoms have been controlled, reducing the dosage to 55 mcg (1 spray in each nostril) once daily may be effective in maintaining control of allergic rhinitis symptoms.
- **Children 2 to 11 Years of Age:** Start with 55 mcg once daily administered as 1 spray (27.5 mcg/spray) in each nostril.[23] Children not adequately responding to 55 mcg may use 110 mcg (2 sprays in each nostril) once daily. Once adequate control is achieved, the dosage may be decreased to 55 mcg once daily.

3. DISEASE DESCRIPTION

EPIDEMINOLOGY

Nasal allergies are one of the most prevalent and chronic diseases in the United States, affecting up to 50 million Americans,[1] including 10 to 30% of adults and up to 40% of children.[2] Approximately 80% of patients diagnosed with allergic rhinitis develop symptoms before the age of 20 years with a peak incidence occurring in children 13 to 14 years of age.[32] Some reports have noted as many as 50% of affected children may first experience symptoms between 2 to 4 years of age.[33] In recent decades, there has been a substantial increase in the prevalence of allergic rhinitis noted to occur in developed countries.[2,34,35]

Several risk factors have been linked to the development of allergic rhinitis including a positive family history of atopic diseases.[36] It is estimated that the risk of allergy increases by 50% when one parent has an atopic history, with the risk increasing to 66% with an atopic history for both parents. Improved sanitation and widespread use of antibiotics have been suggested to be factors for increasing the risk for atopy and allergic disease by altering patterns of immune reactivity.[37,38] Other risk factors for developing allergic rhinitis include higher socioeconomic status, high exposure to indoor allergens such as animal dander and dust mites, higher serum immunoglobulin E (IgE) levels (>100 IU/mL before the age of 6 years), and positive allergen skin-prick tests.[32,36]

PATHOPHYSIOLOGY

In susceptible individuals, inhaled allergens (e.g., pollens in seasonal allergic rhinitis; house-dust mites or animal dander in perennial allergic rhinitis) stimulate the production of allergen-specific immunoglobulin E (IgE) antibodies, which bind to receptors on mast cells in the nasal mucosa.[39,40,41] Upon re-exposure to this allergen, the early-phase reaction, characterized by mast-cell degranulation, occurs within 30 minutes. Intracellular granules fuse with the mast cell membrane and release potent inflammatory mediators into the extracellular environment. The granules contain preformed mediators (e.g., histamine, tryptase, and cytokines) and precursor molecules for the immediate generation of other mediators (e.g., prostaglandins and leukotrienes). These cause vasodilatation and increase vascular permeability, which facilitates the entry of more allergens and cells into tissue spaces, thus amplifying the response.

Effects of mediators are collectively responsible for the symptoms of allergic rhinitis. Histamine causes rhinorrhea and activates sensory nerves to induce pruritis and reflexes such as sneezing. Prostaglandins and leukotrienes cause inflammation and nasal obstruction.

The early phase reaction, reported to occur in over 90% of individuals, may be followed by the late-phase reaction in some patients. In the late-phase reaction, the entire sequence of events recurs 3 to 12 hours later, without additional exposure to allergen. The late phase reaction is also characterized by an influx of inflammatory cells, including eosinophils, basophils, and neutrophils and the subsequent release of their mediators.

CLINICAL PRESENTATION

Rhinitis is inflammation of the nasal mucosa and its accompanying symptoms of rhinorrhea, obstruction, sneezing, and itching.[42] Nasal symptoms are often accompanied by allergic symptoms of the eye that may include itching, tearing and redness (allergic rhinoconjunctivitis), itching of the ears and/or palate, and post-nasal drip.[43] Approximately 60% of patients with allergic rhinitis report having eye symptoms.[44] Allergic rhinitis is the result of exposure to either chronic or seasonal allergens. Seasonal allergic rhinitis (SAR) can occur in the spring or fall. When SAR occurs in the springtime, the triggers are usually tree or grass pollens.[45] Depending on the area of the country, however, symptoms may last from spring through late summer. When symptoms occur in the fall, the trigger is often ragweed. Perennial allergic rhinitis (PAR) occurs year round. Allergens responsible for perennial allergic rhinitis include dust mites, animal dander, and mold spores.

Complications associated with allergic rhinitis include, Eustachian tube dysfunction, sleep disturbances, distorted sense of smell and the consequences of chronic mouth breathing.[39] Chronic rhinitis that is not well-controlled can result in co-morbidities such as sinusitis, otitis media, nasal polyps and asthma.[46] Allergic rhinitis has also been associated with affects on patients' quality of life including fatigue and daytime sleepiness,[3,4] daily activity impairment,[5,6] reduced work productivity,[5,6,7] impaired cognitive functioning,[8,9] reduced learning abilities,[10] impaired sleep, [11] and impaired quality of life.[4]

TREATMENT APPROACHES

Three traditional approaches to controlling allergic rhinitis are avoidance, pharmacotherapy and immunotherapy.[36] Avoidance depends largely on patient awareness of the offending allergen(s) and patient education. Patients should be instructed to avoid environmental allergens that trigger allergy attacks, both at home and at work. This may involve, for example, closing windows to keep pollen out, avoiding outdoor activities, and using air filters and air conditioners.

The second approach is pharmacotherapy. Several classes of drugs are used to treat allergic rhinitis and include antihistamines, decongestants, leukotriene modifiers, cromolyn sodium, ipratropium bromide, and intranasal corticosteroids (INSs).[36] Antihistamines work by blocking the H_1-receptor site and inhibiting the effects of histamine. Antihistamines relieve rhinorrhea, sneezing, itching and ocular symptoms; however in general, they do not effectively relieve nasal obstruction. Many nonprescription antihistamines may cause sedation and anticholinergic side effects, including blurred vision, dry mouth, urinary retention, and constipation.[39] In addition, mental alertness and coordination may be impaired.

Decongestants constrict blood vessels in the nose and reduce mucosal edema to relieve nasal obstruction. They are less effective for rhinorrhea, sneezing and itching. Decongestants are available in topical and oral formulations. Nonprescription decongestants may cause sleeplessness and agitation; topical nasal decongestants can lead to rebound congestion and should therefore, be used for only a few days. Decongestants are often combined with antihistamines to provide relief of all nasal symptoms. This approach is limited because oral decongestants may cause insomnia and agitation and are not recommended for those patients with underlying cardiovascular disease or seizure disorders.[39]

Leukotriene modifiers are a class of drugs used to treat asthma. Of the 3 leukotriene modifier agents available, only montelukast is indicated for the relief of symptoms of seasonal allergic rhinitis. [47] It inhibits one of the many classes of inflammatory mediators, leukotrienes, by binding to leukotriene C_4, D_4, and E_4 receptors. Several large clinical trials[48,49,50] and reviews [51] [52,53] suggest that a leukotriene modifier may not be any more effective, and possibly less so, than non-sedating antihistamines, and are less effective than intranasal corticosteroids.

Intranasal cromolyn sodium is used for the prevention and treatment of the nasal symptoms of allergic rhinitis.[54] Although its mechanism is thought to involve degranulation of mast cells, it has not been fully elucidated.[39] Cromolyn sodium is more effective when used prior to exposure to the allergen. Adverse events associated with its use include sneezing and or nasal stinging.[54]

Intranasal ipratropium bromide is an anticholinergic agent indicated for the symptomatic relief of rhinorrhea associated with allergic and non allergic perennial rhinitis in adults and children 6 years of age and older. [55] It does not relieve nasal congestion, sneezing or post-nasal drip. The most common nasal adverse events reported include epistaxis and nasal dryness.

Intranasal corticosteroid preparations relieve all major nasal symptoms of allergic rhinitis, including nasal obstruction, rhinorrhea, sneezing and itching.[39] These preparations are applied directly to the site of inflammation and inhibit the activity of inflammatory cells and their mediators: histamine, leukotrienes, and prostaglandins. The effectiveness of intranasal corticosteroids depends on regular use. Common adverse events include burning, sneezing, irritation and epistaxis.

The third approach to controlling allergic rhinitis is immunotherapy. [45] A physician may recommend immunotherapy when avoidance and pharmacotherapy fail to provide relief of symptoms.

PLACE IN THERAPY

While INSs have been considered to be the most effective medication class for controlling the symptoms of allergic rhinitis,[42] they have historically failed to demonstrate consistent efficacy in treating the ocular symptoms of itchy, watery, red eyes in patients with SAR. [56,57,58] Studies evaluating the efficacy of an INS to treat ocular symptoms have been retrospective analyses and results have not been replicated in large-scale prospective studies.[59,60,61,62] Thus physicians have been likely to co-prescribed a topical or systemic agent to treat ocular symptoms along with therapy to treat nasal symptoms in patients with allergic rhinitis.[63,36,64]

Veramyst is indicated for the treatment of the symptoms of seasonal and perennial allergic rhinitis in patients 2 years of age and older.(23) *Veramyst* 110 mcg once daily has demonstrated to provide significant improvements in all 4 nasal symptoms (congestion, rhinorrhea, sneezing, and nasal itching) and all 3 ocular symptoms (itching/burning, tearing/watering, redness) associated with SAR in patients 12 years of age and older in 3 prospectively designed and replicated studies.(18,19,20)

4. PRODUCT DESCRIPTION

4.1 Generic Name, Brand Name and Therapeutic Class

GENERIC NAME: fluticasone furoate

BRAND NAME: Veramyst™ Nasal Spray

THERAPEUTIC CLASS: intranasal corticosteroid

4.2 Dosage Forms and Package Sizes

Table 1. *Veramyst*: Dosage Forms/National Drug Code (NDC)/Wholesale Acquisition Cost

Dosage Strength	Description	Package Size	NDC #	WAC*
Nasal spray: 27.5 mcg of fluticasone furoate in each 50- microliter spray	Brown glass bottle enclosed in a nasal device with a small nozzle and a mist-release button to actuate the spray. Each bottle contains a net fill weight of 10g of white, unscented, alcohol-free liquid suspension and will provide 120 metered sprays. The contents of the bottle can be viewed through an indicator window.	1 per box	0173-0753-00	$75.79
*WAC = wholesale acquisition cost effective as of 4/28/2007. WAC is the listed price to wholesalers and warehousing chains, not including prompt pay, stocking or distribution allowances, or other discounts, rebates or charge backs. Store the device in the upright position with the cap in place between 15°-30°C (59°-86F°). Do not freeze or refrigerate. The nasal device should be discarded after 120 sprays have been used.				

4.3 AHFS or Other Drug Classification

DPS/AHFS DRUG CLASSIFICATION: 52:08.08 Corticosteroids

4.4 FDA Approved Indications

FDA APPROVED INDICATION / FDA APPROVAL DATES: *Veramyst* Nasal Spray is an intranasal corticosteroid indicated for treatment of symptoms of seasonal and perennial allergic rhinitis in adults and children ≥2 years: April 28, 2007.

4.5 Use in Special Populations

Refer to Enclosed Prescribing Information.

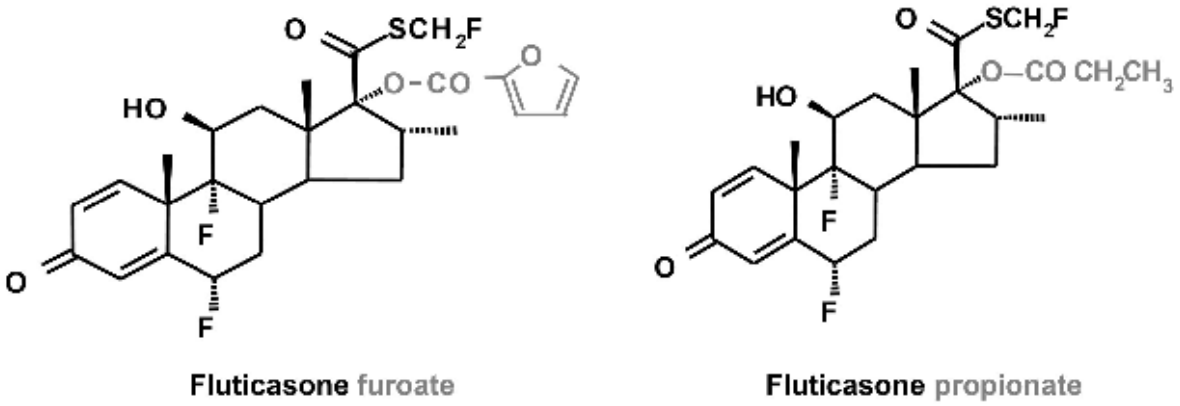
4.6 Pharmacology

Refer to Enclosed Prescribing Information.

Structural Characteristics

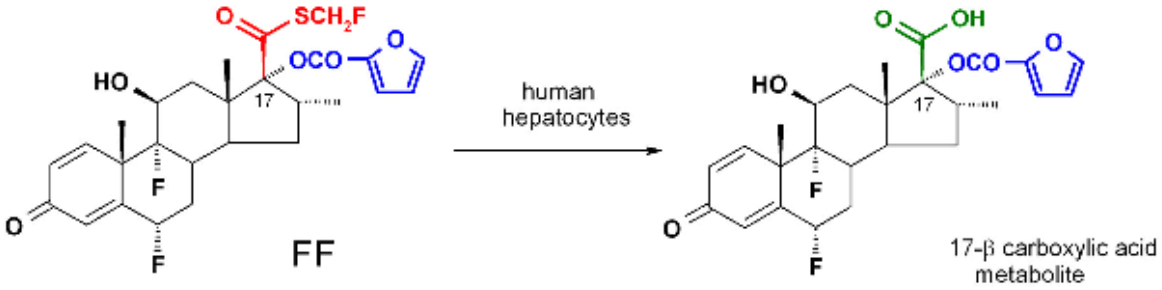
Fluticasone furoate (FF) is a synthetic trifluorinated corticosteroid with potent anti-inflammatory activity.[23] FF is characterized by the combination of the 17α-furoate ester with the 17β-fluoromethylthioester on the fluticasone steroid template (Figure 1).[65] The furoate ester of FF replaces the propionate of fluticasone propionate (FP). FF is metabolically stable and is only active in the body as the intact molecule. The 17α-position furoate ester of the molecule is not removed. FF is not a prodrug nor an alternative salt of fluticasone.

Figure 1. Fluticasone Furoate and Fluticasone Propionate Chemical Structures



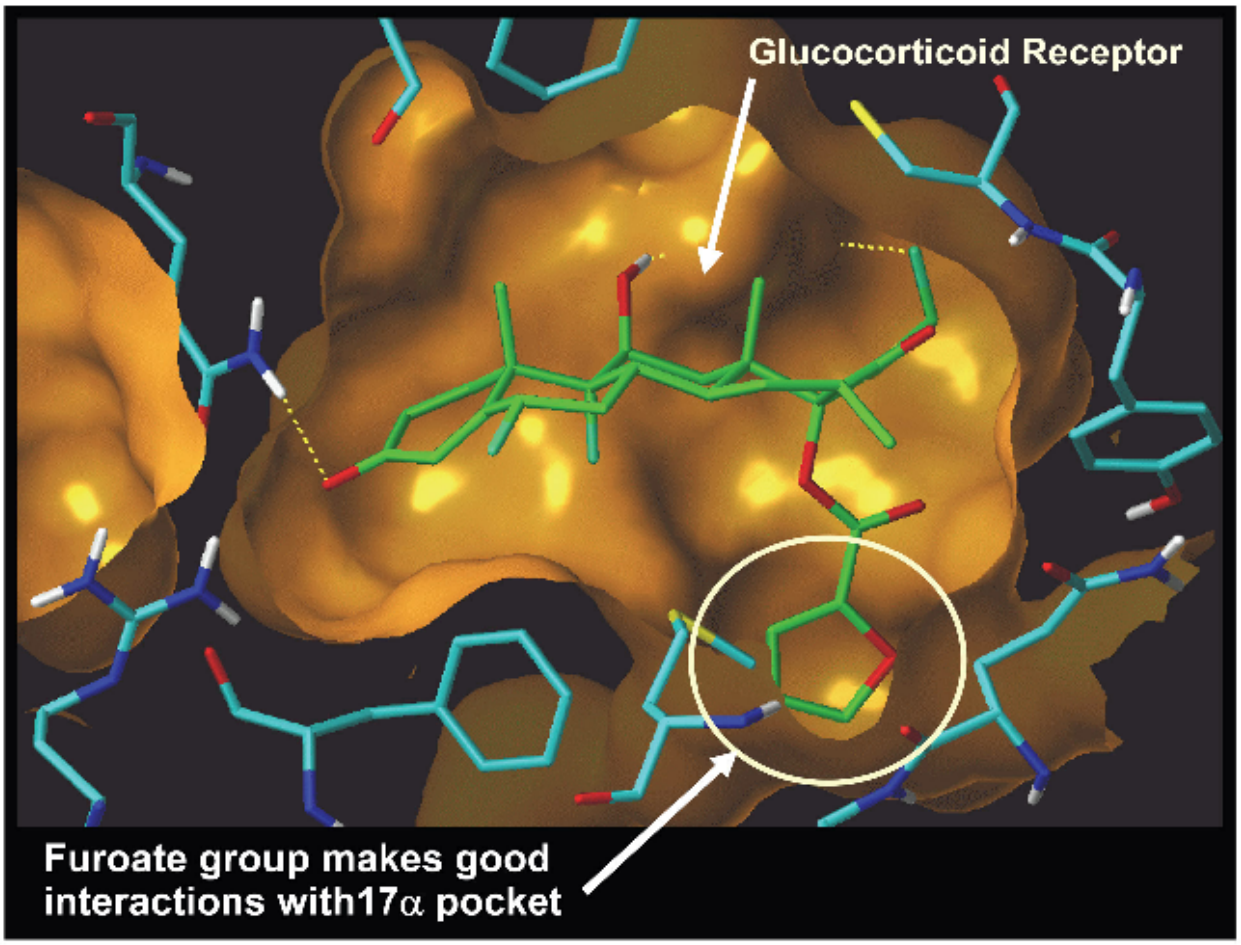
FF is rapidly metabolized and inactivated in the liver once it enters systemic circulation.[65] The molecule is inactivated via the removal of the 17β-fluoromethylthioester (a different ester group from the furoate ester) to the inactive 17β-carboxylic acid metabolite (Figure 2).

Figure 2. Metabolism of Fluticasone Furoate to the Inactive Metabolite



X-ray crystallography studies with the human glucocorticoid receptor (GR) show that the 17α-position furoate ester and the steroid backbone of FF make a series of key contacts with the amino acid residues in the glucocorticoid receptor binding site (Figure 3).[66] The furoate moiety has been shown to fully occupy the lipophilic 17α pocket which may explain the enhanced glucocorticoid receptor affinity of FF.

Figure 3. Fluticasone Furoate in the Glucocorticoid Receptor*



* x-ray study at 2.9Angs resolution

Receptor Characteristics

Glucocorticoid Receptor Binding

It is hypothesized that glucocorticoids exert their effects by binding to glucocorticoid receptors (GR), which are predominantly localized to the cytoplasm of target cells. [67] Upon binding to the GR, the GR-glucocorticoid complex is then translocated into the nuclear department where it binds to specific DNA glucocorticoid response element (GRE) binding sites which regulate the transcription of a variety of anti-inflammatory gene products.

Preclinical studies showed fluticasone furoate to have a higher affinity for the human glucocorticoid receptor than many currently available glucocortiocoids. The glucocorticoid receptor binding kinetics of fluticasone furoate demonstrated a relative receptor affinity (RRA) of 2989 ± 135 with reference to dexamethasone (RRA: 100 ± 5).[68] Other corticosteroids displayed a significantly lower receptor affinity: mometasone furoate (MF) 2244 ± 142, fluticasone propionate (FP) 1775 ± 130, beclomethasone-17-monopropionate (17-BMP) 1345±125, ciclesonide active principle (CIC-ap) 1212 and budesonide 855 (Table 2).

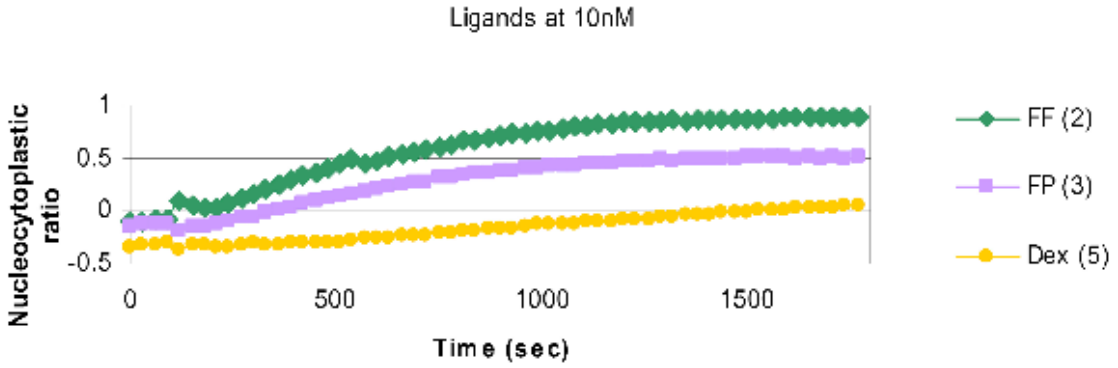
Table 2. Glucocorticoid Receptor Binding Comparisons

Glucocorticoid	Relative receptor affinity ± SD
Dexamethasone	100 ± 5
Budesonide	855 ± 5
Ciclesonide (active principle)	1212 ± 5
Beclomethasone-17-monopropionate	1345±125
Fluticasone propionate	1775 ± 130
Mometasone furoate	2244 ± 142
Fluticasone Furoate	2989 ± 135

Glucocorticoid-Induced Translocation

FF causes a rapid translocation of the glucocorticoid receptor to its nuclear site of action which may hasten the onset of glucocorticoid action (Figure 4).[69]

Figure 4. Rate of Glucocorticoid Receptor Nuclear Translocation from Cytoplasm to the Nucleus



FF causes a rapid translocation of GR to its nuclear site

* *In vitro* activity does not necessarily correlate with clinical response. Comparative clinical conclusions based on these data can not be made.

Receptor Selectivity

An *in vitro* study showed FF to have a high selectivity for the glucocorticoid receptor compared with other closely related steroid hormone receptors (Table 3).[69] FF showed better steroid hormone selectivity than mometasone furoate or ciclesonide-active principle.

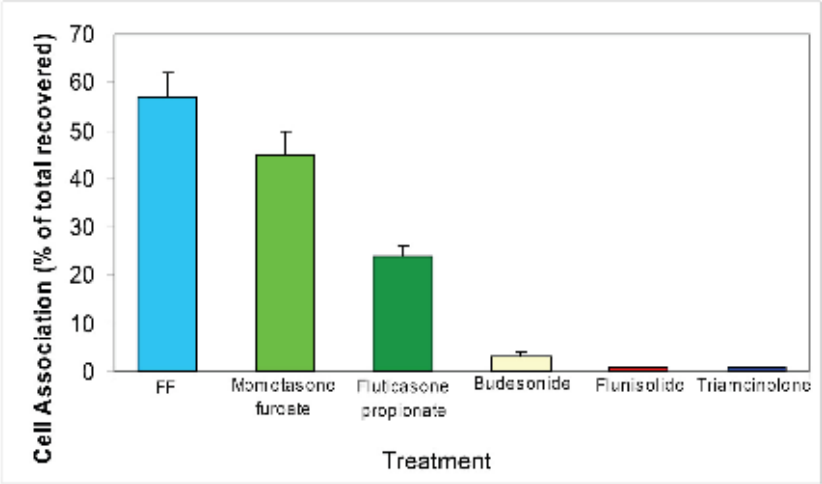
Table 3. Human Steroid Hormone Selectivity (fold difference compared to GR)

Steroid Receptor	FF	FP	Mometasone Furoate	Ciclesonide active principle
Glucocorticoid	1	1	1	1
Mineralocorticoid	794	631	20	10
Progesterone	38	29	0.8	20
Androgen	>300 000	>30 000	>5000	-
Estrogen	>300 000	>25 000	400 000	>50 000

Binding to Respiratory Tissue

An *in vitro* study in human lung epithelial cells showed fluticasone furoate binds more avidly to respiratory tissue than other glucocorticoids measured ().[69]

Figure 5. Binding to Human Lung Epithelial Cells



Inhibitory Potency

Many pro-inflammatory cytokines are regulated by NFκB, hence NFκB inhibition gives an indication of potency against these genes. As shown in Figure 6 and Figure 7, fluticasone furoate showed very high potency for inhibition of the pro-inflammatory transcription factor NFκB and inhibition of the pro-inflammatory cytokine TNFα.[69] Fluticasone furoate is a very effective inhibitor of inflammatory mediators *in vitro* with greater affinity than FP.

Figure 6. Inhibitory Potency (IC_{50}) Against TNFα-Induced NFκB Activity in Human Lung Epithelial Cells

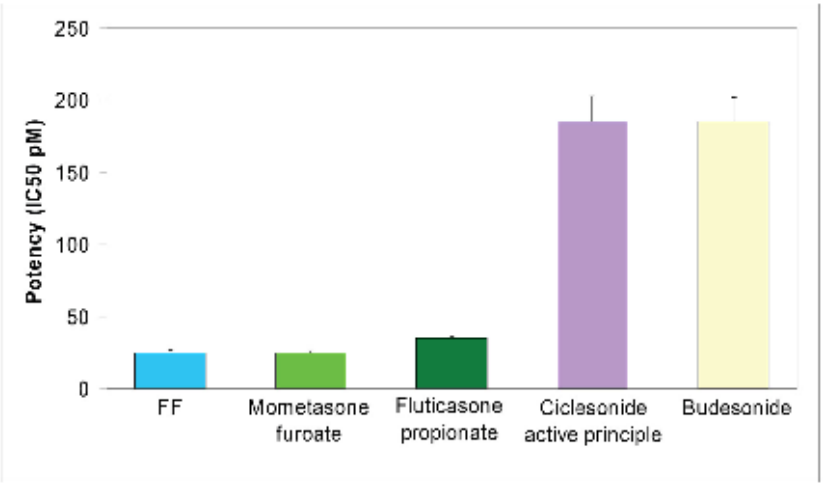
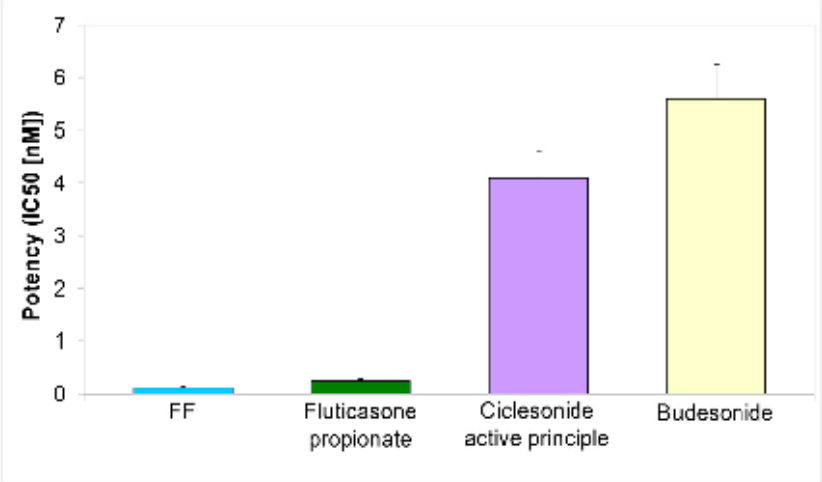
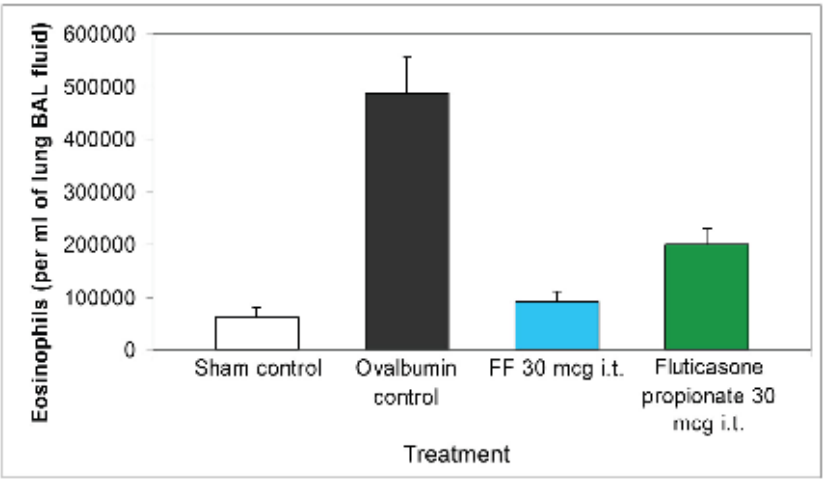


Figure 7. Inhibitory potency (IC_{50}) against Lipolysaccharide (LPS)-induced TNFα release from Human Peripheral Blood Mononuclear Cells



The Brown Norway rat model was used to assess the effects of fluticasone furoate on inhibition of lung eosinophilia. Lung eosinophilia was induced by administration of intracheal (it) ovalbumin. Assessment of eosinophils in the bronchoalveolar lavage (BAL) fluid was performed following administration of glucocorticoids. Significant inhibition of eosinophilia was achieved after administration of fluticasone furoate and the response was greater than that seen with fluticasone propionate (Figure 8).[69]

Figure 8. Effect of FF and FP on Eosinophil Influx in the Brown Norway Rat Model of Inflammation



4.7 Mechanism of Action for Relief of Ocular Symptoms

Background

An association exists between rhinitis and conjunctivitis.[63] A possible mechanism to explain this association is the naso-conjunctival reflex. It is known that naso-conjunctival reflexes may produce ocular symptoms in patients with seasonal allergic rhinitis, and nasal symptoms in patients with conjunctivitis. It is also known that several forms of rhinoconjunctivitis treatment of the nose also improves eye symptoms.

Reflex mechanisms within the nose have been shown to occur in response to nasal challenge with an antigen.[70] Nasal challenge with an antigen has been shown to induce a reflex in the contralateral nasal cavity. This reflex is known as the naso-nasal reflex. The contralateral response to an antigen has been demonstrated to be blocked by topical anticholinergic agents applied to the contralateral nostril, suggesting that the efferent limb is parasympathetically mediated. Histamine is only released on the side of the nasal antigen challenge. However, oral antihistamines reduce the contralateral response to unilateral

nasal allergen challenge, suggesting that histamine contributes to the initiation of the reflex. As the eye is richly innervated by parasympathetic nerves, the conjunctiva may respond to the nasal allergen in a manner similar to that demonstrated in the contralateral nasal cavity.

Clinical Information

A placebo controlled, 2-way crossover study in 20 healthy patients with a history of grass and/or ragweed allergy was conducted to test the hypothesis of a possible neurogenic reflex mechanism between the nose and eye.(71) Patients underwent skin prick tests to confirm a ragweed allergy and then a nasal allergen challenge at screening. Responders were randomized to receive pretreatment with either an intranasal antihistamine or placebo and then underwent nasal challenge in 1 nostril with a diluent and 1 dose of an allergen 10 minutes after pretreatment. Two weeks later, subjects crossed over to the other treatment. The results showed that unilateral nasal challenge led to a naso-nasal reflex and increased nasal secretions in both nostrils. Additionally increased lacrimation in both eyes was noted. Eye symptoms were reduced significantly by antihistamine pretreatment and secretions within the eyes were reduced, but not significantly.

The investigators suggested that the naso-ocular reflex is increased by allergic inflammation and supports the hypothesis that the anti-inflammatory effects of fluticasone furoate on the nasal mucosa may decrease the strength of the naso-ocular reflex, leading to a reduction in allergic eye symptoms.

4.8 Pharmacokinetics/Pharmacodynamics

Refer to Enclosed Prescribing Information.

Absorption

Bioavailability

Sixteen healthy male and female subjects aged 19 to 45 years, participated in a single-center, randomized, open-label, 2-period crossover study to estimate the absolute bioavailability of fluticasone furoate.(23,72) Each subject received supratherapeutic dosages of fluticasone furoate 880 mcg given intranasally at 8 hour intervals for 10 doses (2640 mcg/day) in the first treatment period followed by a single intravenous dose of 250 mcg over 20 minutes in the second treatment period. The two treatment periods were separated by a 4 to 5 day washout period. Blood samples were collected at numerous time points around the final dose to determine the plasma concentration of fluticasone furoate. The geometric mean of the absolute bioavailability was 0.5% (90% CI: 0.34%, 0.74%).

Due to the low bioavailability by the intranasal route, the majority of the pharmacokinetic data for fluticasone furoate was obtained via other routes of administration.(23) Studies using oral solution and intravenous dosing of radiolabeled drug, demonstrated that at least 30% of fluticasone furoate was absorbed and then rapidly cleared from plasma. Oral bioavailability was on average 1.26%, and the majority of the circulating radioactivity was due to inactive metabolites.

Plasma concentration following Intranasal Administration

The activity of *Veramyst* is due to the parent drug, fluticasone furoate. Following intranasal administration of fluticasone furoate, most of the dose is eventually swallowed and undergoes incomplete absorption and extensive first pass metabolism in the liver and gut, resulting in negligible systemic exposure.(23) At the highest recommended intranasal dosage of 110 mcg once daily for up to 12 months in adults and up to 12 weeks in children, plasma concentrations of fluticasone furoate are typically not quantifiable despite the use of a sensitive HPLC MS/MS assay with a lower limit of quantification (LOQ) of 10 pg/mL. However, in a few isolated cases (<0.3%) fluticasone furoate was detected in high concentrations above 500 pg/mL, and in a single case the concentration was as high as 1,430 pg/mL in the 52 week study. There was no relationship between these concentrations and cortisol levels in these subjects. The reasons for these high concentrations are unknown.

Plasma pharmacokinetic parameters were determined in 16 healthy subjects following intranasal administration of fluticasone furoate 880 mcg at 8-hour intervals for 10 doses.(72) Table 4.

Table 4. Pharmacokinetic Parameters following Intranasal Administration(72)

Parameter	n	Geometric Mean (95% CI)
AUC_{0-t}, pg/mL/h	14*	74.92 (43.64-128.63)
$AUC_{0-\tau}$, pg/mL/h	8†	136.31 (90.72-204.81)
C_{max}, pg/mL	15‡	20.53 (16.04-26.27)
MRT, h	14*	2.743 (1.943-3.873)
		Median (range)
T_{max}, median hour	15‡	0.75 (0.08-8)
AUC_{0-t} =area under concentration-time curve up to last non-zero value; $AUC_{0-\tau}$ = area under the curve from time 0 to the end of the dosing interval; C_{max} = maximum plasma concentration; T_{max} = time to reach first occurrence of C_{max}; MRT = mean residence time; *=Two subjects had ≤1 measurable plasma concentration; †= Eight subjects had no measurable plasma concentration at 8 hours after administration; ‡= One subject had no measurable concentration		

Distribution

Following intravenous administration, the mean volume of distribution at steady state is 608 L.(23) Binding of fluticasone furoate to human plasma proteins is greater than 99%.

Tissue concentrations, such as ocular or lacrimal concentrations, following the intranasal administration of recommended doses of *Veramyst* in humans have not been determined. Given the low systemic bioavailability (0.5%) of fluticasone furoate and high volume of distribution, drug concentrations in specific tissue sites would likely be well below the current assay detection limit of 10 pg/mL.

Metabolism

Fluticasone furoate is a distinct drug molecule and not a salt or a prodrug of fluticasone.(65) In vivo studies have revealed no evidence of cleavage of the furoate moiety to form fluticasone.(23) Fluticasone furoate is cleared (total plasma clearance of 58.7 L/h) from systemic circulation principally by hepatic metabolism via the cytochrome P450 isozyme CYP3A4. The principal route of metabolism is hydrolysis of the S-fluoromethyl carbothioate function to form the inactive 17β carboxylic acid metabolite.

Excretion

In an open, non-randomized cross-over study, five healthy males aged 50-56 years received a single 2 mg dose of fluticasone furoate orally followed by an intravenous infusion of 250 mcg of fluticasone furoate over 30 minutes.(23) The two doses were separated by at least a 28-day period. Fluticasone furoate and its metabolites were eliminated primarily in the feces, accounting for approximately 100% and 90% of the 2 mg orally and 250 mcg intravenously administered dose, respectively. The majority of the drug was recovered within 72 hours. Urinary excretion accounted for approximately 1% and 2% of the orally and intravenously administered dose, respectively. The elimination phase half life averaged 15.1 hours (95% CI: 11.82 to 19.35 hours) following intravenous administration.

Special Populations

Elderly

In clinical trials, only a small number of elderly subjects (n=23/872; 2.6%) provided pharmacokinetic data. There was no evidence to suggest that the presence or absence of detectable levels of fluticasone furoate was related to gender, age, or race.(23) Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

Children

Fluticasone furoate is typically not quantifiable following intranasal dosing of 110 mcg once daily.(23) Quantifiable levels (>10 pg/mL) were observed in <31% of patients aged 12 years and older and in <16% of children (aged 2 to 11 years) following intranasal dosing of 110 mcg once daily and in <7% of children following intranasal dosing of 55 mcg once daily. There was no evidence to suggest that the presence or absence of detectable levels of fluticasone furoate was related to gender, age, or race.

Renal Impairment

Fluticasone furoate is not detectable in urine from healthy volunteers after intranasal dosing.[23] Less than 1% of dose-related material is excreted in urine and therefore renal impairment would not be expected to affect the pharmacokinetics of fluticasone furoate. No dosage adjustment is required in patients with renal impairment.

Hepatic Impairment

Reduced liver function may affect the elimination of corticosteroids.[23] Since fluticasone furoate undergoes extensive first pass metabolism by the hepatic cytochrome P450 isozyme CYP3A4, the pharmacokinetics of fluticasone furoate may be altered in patients with hepatic impairment. A study of a single 400 mcg dose of *orally inhaled* fluticasone furoate in patients with moderate hepatic impairment (Child Pugh Class B) resulted in increased C_{max} (42%) and $AUC_{(0-\infty)}$ (172%), resulting in an approximately 20% reduction in serum cortisol level in patients with hepatic impairment compared to healthy subjects. The systemic exposure would be expected to be higher than that observed had the study been conducted after multiple doses and/or in patients with severe hepatic impairment. Therefore, *Veramyst* should be used with caution in patients with severe hepatic impairment.

Onset of Action of Veramyst in Adult and Adolescents

Seasonal Allergic Rhinitis

Table 5 summarizes the onset of action following the administration of *Veramyst* 110 mcg QD in patients 12 years of age and older with SAR. Study 1 demonstrated a statistically significant difference for *Veramyst* compared with vehicle placebo for the iTNSS assessments at 8 and 10 hours. [73] A statistically significant difference was not seen at 12 hours in Study 1 but was demonstrated at 24 hours and then sustained throughout the remainder of the study. In a dose-ranging study (Study 4) similar results were reported for *Veramyst* 110 mcg QD with statistical significance achieved at 8, 12 and 24 hours, and sustained throughout the remaining 14 days. [74] In Study 2, the least square mean change from baseline in iTNSS was numerically greater at all post-dose time points assessed on Day 1, reached statistical significance at 24 hours, and was maintained throughout the remainder of the study. [75] The least square mean difference in iTNSS in Study 3 between the two treatments was not statistically significant until 24 hours after the first dose and was maintained throughout the treatment period except on Days 3 and 5. [76]

Time to onset was also assessed by the mean change from baseline in the daily rTNSS on Days 1 through 14. In Studies 1, 2 and 4, statistically significant reductions in daily rTNSS occurred following treatment with *Veramyst* 110 mcg on Day 1 ($P < 0.05$) and was sustained throughout Day 14 ($P < 0.001$). [73] [75,74] In Study 3, the mean difference between the two treatments in daily rTNSS achieved statistical significance at Day 7 ($P = 0.036$) and was sustained throughout Day 14 ($P \leq 0.014$). [76] Weather-related effects on pollen possibly contributed to this outcome.

Time to onset was supported by the mean change from baseline in the PM and AM rTNSS on Days 1 through 14. Statistically significant reductions in the PM rTNSS occurred in Studies 1, 2 and 4 at Day 1 at the 12-hour time point and were sustained through Day 14 of treatment. Statistically significant reductions in AM rTNSS occurred in Studies 2 and 4 at Day 1 and in Study 1 at Day 2 ($P < 0.001$). Significance was sustained throughout the remainder of the treatment period ($P < 0.001$). In Study 3, statistical significance was not achieved until Day 8 ($P = 0.002$) and Day 6 ($P = 0.032$) for PM rTNSS and AM rTNSS, respectively, however both measures were sustained through Day 14 ($P \leq 0.049$). Weather-related effects on pollen possibly contributed to this outcome.

Table 5. Onset of Action of *Veramyst* in Adult and Adolescents with SAR [73] [75] [76] [74]

	Vehicle Placebo	***Veramyst* 110 mcg QD**		
Study:				
1 Ragweed	**(n=148)**	**(n=151)**		
2 Grass	**(n=144)**	**(n=141)**		
3 Mountain Cedar	**(n=150)**	**(n=152)**		
4 Mountain Cedar*	**(n=128)**	**(n=127)**		
LS Mean Change from Baseline in:	**LS Mean Change**	**LS Mean Change**	**LS Mean Difference (95% CI)**	***P* Value**
iTNSS post-dose-8 hours				
Study 1	**-2.2**	**-2.89**	**-0.696 (-1.32, -0.07)**	**0.028**
Study 2	-3.03	-3.56	-0.529 (-1.17, 0.11)	0.105
Study 3	-2.44	-2.63	-0.192 (-0.74, -0.36)	0.492
Study 4	**-2.32**	**-3.03**	**-0.71 (-1.36, -0.06)**	**0.032**
iTNSS post-dose-10 hours				
Study 1	**-2.14**	**-2.91**	**-0.763 (-1.39, -0.14)**	**0.017**
Study 2	-3.02	-3.62	-0.600 (-1.27, 0.07)	0.078
Study 3	-2.48	-2.75	-0.269 (-0.86, 0.32)	0.367
Study 4	--	--	--	--
iTNSS post-dose-12 hours				
Study 1	-1.99	-2.5	-0.507 (-1.15, 0.13)	0.12
Study 2	-2.8	-3.46	-0.654 (-1.34, 0.04)	0.064
Study 3	-2.53	-2.88	-0.347 (-1.00, 0.31)	0.297
Study 4	**-2.12**	**-3.21**	**-1.089 (-1.76, -0.42)**	**0.001**
iTNSS post-dose-24 hours				
Study 1	**-1.06**	**-1.81**	**-0.751 (-1.28, -0.22)**	**0.006**
Study 2	**-1.45**	**-2.69**	**-1.244 (-1.81, -0.68)**	**<0.001**
Study 3	**-0.92**	**-1.46**	**-0.535 (-1.06, -0.01)**	**0.045**
Study 4	**-0.71**	**-1.94**	**-1.232 (-1.8, -0.67)**	**<0.001**
LS=least square, CI=Confidence Interval, iTNSS= instantaneous total nasal symptom score, *Dose-ranging study				

Perennial Allergic Rhinitis

In a 4-week clinical trial in adult and adolescent patients with PAR, a statistically significant treatment difference (least square mean difference from baseline) in AM pre-dose iTNSS between *Veramyst* and vehicle placebo was first observed on Day 4 ($P = 0.028$). [77] Statistical significance was maintained

throughout the treatment period ($P \leq 0.045$), except for Days 7, 16, 24, 25, and 26. A statistically significant treatment difference (least square mean difference from baseline) assessed by daily rTNSS occurred on Day 4 ($P = 0.014$) and was maintained throughout the treatment period ($P \leq 0.049$), except for Days 7, 8, 10, and 25. The least square mean difference between the two treatments in mean PM rTNSS for Days 1 to 28 achieved statistical significance on Day 14 ($P = 0.004$) and was sustained through Day 28 ($P \leq 0.041$), except for Days 21, 23, 25, and 27. The least square mean difference between the two treatments in mean AM rTNSS for Days 1 to 28 achieved statistical significance on Day 4 ($P = 0.007$) and was sustained through Day 28 ($P \leq 0.032$), except for Days 7, 8, 10, 21, 24, 25 and 27.

Onset of Action of Veramyst in Children

Seasonal Allergic Rhinitis

A pediatric clinical trial assessed the onset of treatment effect for patients 6 to 11 years of age with SAR.[78] A statistically significant treatment difference in mean change from baseline for AM pre-dose iTNSS was demonstrated on Day 6 ($P = 0.035$) for *Veramyst* 110 mcg compared with vehicle placebo, which was maintained throughout the treatment period ($P \leq 0.044$), except for Day 14. A statistically significant treatment difference in mean change from baseline for AM pre-dose iTNSS was only observed on Day 12 ($P = 0.040$) for *Veramyst* 55 mcg.

A statistically significant treatment difference in mean change from baseline for daily rTNSS was first observed on Day 4 ($P = 0.046$) for *Veramyst* 110 mcg, which was maintained throughout the treatment period ($P \leq 0.046$), except for Days 5, 9, 10, and 14. A statistically significant treatment difference in mean change from baseline for daily rTNSS for *Veramyst* 55 mcg was only observed on Day 12 ($P = 0.044$).

The mean difference between the two treatments in mean AM rTNSS for Days 1 to 14 achieved significance on Day 4 ($P = 0.031$) and was sustained through Day 14 ($P \leq 0.039$), except for Days 5, 9, 10 and 14 for *Veramyst* 110 mcg QD. For patients receiving *Veramyst* 55 mcg, the mean difference between the two treatments in mean AM rTNSS did not achieve statistical significance on any day. The mean difference between the two treatments in mean PM rTNSS for Days 1 to 14 achieved statistical significance on Day 7 ($P = 0.028$) and was sustained through Day 13 ($P \leq 0.049$) for *Veramyst* 110 mcg. Treatment with *Veramyst* 55 mcg achieved significance only on Day 12 ($P = 0.027$).

Perennial Allergic Rhinitis

In pediatric patients aged 6 to 11 years of age with PAR, a statistically significant treatment difference in mean change from baseline for AM pre-dose iTNSS between *Veramyst* 110 mcg and vehicle placebo was first observed on Day 3 ($P = 0.024$) and then on Day 7 ($P = 0.038$), Day 8 ($P = 0.039$), Day 10 ($P = 0.044$), and Day 16 ($P = 0.038$). [79] Statistical significance was maintained from Day 16 through Day 28 ($P \leq 0.038$) with the exception of Day 27. A statistically significant treatment difference in mean change from baseline for AM pre-dose iTNSS between *Veramyst* 55 mcg and vehicle placebo was first observed on Day 5 ($P = 0.037$) and then on Day 10 ($P = 0.017$). Statistical significance was maintained from Day 10 through Day 28 ($P \leq 0.017$) with the exception of Days 12–15.

A statistically significant treatment difference in mean change from baseline for daily rTNSS between *Veramyst* 110 mcg and vehicle placebo was first observed on Day 18 ($P = 0.015$) and then again on Days 21, 22, and 28 ($P \leq 0.039$). A statistically significant treatment difference in mean change from baseline for daily rTNSS between *Veramyst* 55 mcg and vehicle placebo was first observed on Day 6 ($P = 0.022$) and significance was maintained from Day 6 through Day 28 ($P \leq 0.033$) with the exception of Days 8, 9, 14, and 15.

The mean difference between the two treatments in mean AM rTNSS for Days 1 to 28 achieved statistical significance on Days 18, 19, and 28 ($P = 0.028, 0.050, 0.024$, respectively) for *Veramyst* 110 mcg QD. For *Veramyst* 55 mcg, the mean difference between the two treatments in mean AM rTNSS achieved statistical significance on Day 6 ($P = 0.040$) and was sustained until Day 28 ($P \leq 0.021$) except for Days 7, 8, 9, 13, 14, and 15. The mean difference between the two treatments in mean PM rTNSS for Days 1 to 28 achieved statistical significance on Days 18, 21, 22, 25, and 28 ($P = 0.024, 0.020, 0.011, 0.042, 0.047$) for *Veramyst* 110 mcg. Treatment with *Veramyst* 55 mcg achieved statistical significance on Day 6 ($P = 0.031$) and was sustained until Day 28 ($P \leq 0.035$) except on Days 14 and 15.

4.9 Contraindications

Refer to Enclosed Prescribing Information.

4.10 Warnings/Precautions

Refer to Enclosed Prescribing Information.

4.11 Adverse Reactions in Adults and Adolescents

Refer to Enclosed Prescribing Information.

Short-Term Clinical Trial Experience

Overall adverse reactions were reported with approximately the same frequency by patients treated with *Veramyst* as those receiving placebo in 6 clinical trials of 2 to 6 weeks' duration. [23] Less than 3% of patients in clinical trials discontinued treatment because of adverse reactions. The rate of withdrawal among patients treated with *Veramyst* was similar or lower than the rate among placebo-treated patients. Common adverse reactions that occurred more frequently in patients 12 years of age and older treated with *Veramyst* compared with placebo-treated patients are listed in Table 6.

Table 6. Adverse Reactions with >1% Incidence in Controlled Clinical Trials of 2 to 6 weeks' Duration with *Veramyst* in Patients with Seasonal or Perennial Allergic Rhinitis

Adverse Event	Adults and Adolescent Patients 12 Years of Age and Older	
	Vehicle Placebo (n=774)	*Veramyst* 110 mcg Once Daily (n=768)
Headache	54 (7%)	72 (9%)
Existaxis	32 (4%)	45 (6%)
Pharynolaryngeal pain	8 (1%)	15 (2%)
Nasal ulceration	3 (<1%)	11 (1%)
Back pain	7 (<1%)	9 (1%)

Long-Term Clinical Study Experience

In a 52-week, long-term safety trail in adults and adolescents 12 years of age and older with perennial allergic rhinitis, *Veramyst* 110 mcg once daily (n=605) was compared with vehicle placebo (n=201). [23] Adverse reactions were similar in type and rate between the treatment groups. However, epistaxis occurred more frequently in patients receiving *Veramyst* (123/605, 20%) than in the placebo group (17/201, 8%). The episodes of epistaxis were of mild intensity in the majority of patients (17/17 in the placebo group and 83/123 in the group receiving *Veramyst*). The episodes were of moderate intensity in 39 patients and of severe intensity in 1 patient receiving *Veramyst*. No patient experienced a nasal septal perforation during the trial.

4.12 Adverse Reactions in Pediatric Patients

Refer to Enclosed Prescribing Information.

Short-Term Clinical Trial Experience

Overall adverse reactions were reported with approximately the same frequency by pediatric patients treated with *Veramyst* as those receiving placebo in 3 clinical trials of 2 to 12 weeks' duration.[23] Common adverse reactions that occurred more frequently in patients 2 to 11 years of age treated with *Veramyst* compared with placebo are listed in Table 7.

Table 7. Adverse Reactions with >3% Incidence in Controlled Clinical Trials of 2 to 12 weeks' Duration with *Veramyst* in Pediatrics with Seasonal or Perennial Allergic Rhinitis

Adverse Event	Pediatric Patients Aged 2 to <12 Years of Age		
	Vehicle Placebo (n=429)	*Veramyst* 55 mcg Once Daily (n=369)	*Veramyst* 110 mcg Once Daily (n=426)
Headache	31 (7%)	28 (8%)	33 (8%)
Nasopharyngitis	21 (5%)	20 (5%)	21 (5%)
Existaxis	19 (4%)	17 (5%)	17 (4%)
Pyrexia*	7 (2%)	17 (5%)	19 (4%)
Pharynolaryngeal pain	14 (3%)	16 (4%)	12 (3%)
Cough	12 (3%)	12 (3%)	16 (4%)
*Pyrexia occurred more frequently in children 2 to <6 years of age compared with children 6 to <12 years			

4.13 Drug/Food/Disease Interactions

Refer to Enclosed Prescribing Information.

4.14 Dosing and Administration

Refer to Enclosed Prescribing Information.

5. PIVOTAL EFFICACY AND SAFETY TRIALS

5.1 Background

Background for Efficacy Assessments

Evaluation of Nasal Symptoms

The evaluation of nasal symptoms and assessment of efficacy for *Veramyst* was based on the total nasal symptom score (TNSS).[23] TNSS was calculated as the sum of patient- or parent/guardian-rated scoring of 4 individual nasal symptoms (rhinorrhea, nasal congestion, sneezing, and nasal itching) on a 0 to 3 categorical severity scale (0 = absent, 1 = mild, 2 = moderate, 3 = severe) as reflective or instantaneous. Reflective TNSS (rTNSS) required the patients or guardians to record symptom severity over the previous 12 hours; the instantaneous TNSS (iTNSS) required patients or guardians to record symptom severity at the time immediately prior to the next dose. Morning and evening rTNSS scores were averaged for the daily TNSS. The mean change from baseline in daily rTNSS was the primary efficacy endpoint. The morning iTNSS (AM iTNSS), evaluated immediately prior to the AM dose, reflects the TNSS at the end of the 24 hour dosing interval and is an indication of whether the effect was maintained over the 24 hour dosing interval.

Evaluation of Ocular Symptoms

The evaluation of ocular symptoms and assessment of efficacy for *Veramyst* was based on total ocular symptom score (TOSS).[23] TOSS was calculated based on patient- or parent/guardian-rated scoring of 3 individual eye symptoms (itching/burning, tearing/watering, and redness) on a 0 to 3 categorical severity scale (0 = absent, 1 = mild, 2 = moderate, 3 = severe) as reflective or instantaneous. Assessment of ocular efficacy, daily rTOSS and AM pre-dose iTOSS, were evaluated as described above for TNSS.

Other Efficacy Parameters

Additionally, an overall evaluation of response to therapy (ORT) was assessed at the end of the study by the patient or parent/guardian.[18] The ORT was rated on a 7-point categorical scale: significantly improved, moderately improved, mildly improved, no change, mildly worse, moderately worse, and significantly worse.

5.2 Pivotal Efficacy and Safety Trials with *Veramyst* in Adult and Adolescent Patients with Seasonal Allergic Rhinitis

Pivotal Efficacy and Safety Studies

The efficacy and safety of *Veramyst* 110 mcg once daily was evaluated in three, 2-week, randomized, double-blind, placebo-controlled studies. Studies 1 (N=299)[73], 2 (N=285)[75], and 3 (N=302)[76] included patients 12 years of age and older who had a diagnosis of seasonal allergic rhinitis (SAR) due to ragweed, grass pollen, or mountain cedar, respectively.

Primary and Key Secondary Efficacy Measures

Assessment of efficacy was based on the total nasal symptom score (TNSS) and the total ocular symptoms score (TOSS). TNSS was calculated based on the sum of a patient's score for the four individual nasal symptoms (rhinorrhea, nasal congestion, sneezing, and nasal itching), which were rated on a 0-3 categorical severity scale. TOSS was also calculated based on the sum of a patient's three ocular symptoms (itching/burning, tearing/watering, and redness) assessed on a 0-3 categorical severity scale. Both nasal and ocular symptoms were rated by the patient.

The primary efficacy endpoint was the mean change from baseline over the entire treatment period in the daily reflective, total nasal symptom score (rTNSS). The rTNSS was defined as the average of the daytime and nighttime total nasal symptom scores, evaluated over 12-hour intervals.

Key secondary endpoints included the mean change from baseline over the entire treatment period in the morning, pre-dose, instantaneous, total nasal symptom score (iTNSS). The morning iTNSS was defined as the score at the end of the 24-hour dosing interval performed at the moment immediately prior to taking the next daily dose. Another key secondary endpoint was the mean change from baseline over the entire treatment period in reflective, total ocular symptom scores (rTOSS).

Additionally, an overall evaluation of response to therapy (ORT) was assessed at the end of the study by the patient. The ORT was rated on a 7-point categorical scale ranging from significantly improved to significantly worse.

Results

For the primary efficacy endpoint of mean change from baseline over the entire treatment period in daily rTNSS, *Veramyst* 110 mcg was significantly more efficacious ($P \leq 0.003$) in reducing the nasal symptoms of SAR versus vehicle placebo in all three studies (Figure 9). Additionally, the mean differences for AM rTNSS and PM rTNSS were also significant for *Veramyst* compared with placebo ($P \leq 0.007$).

Veramyst 110 mcg was also significantly more efficacious than placebo for the three key secondary endpoints: mean change from baseline in AM pre-dose iTNSS (Figure 10), mean change from baseline in daily rTOSS (Figure 11), and the overall evaluation of response to therapy (Figure 12).

Figure 9. Mean Change from Baseline in Daily Reflective Total Nasal Symptoms Scores Across 3 Pivotal Studies

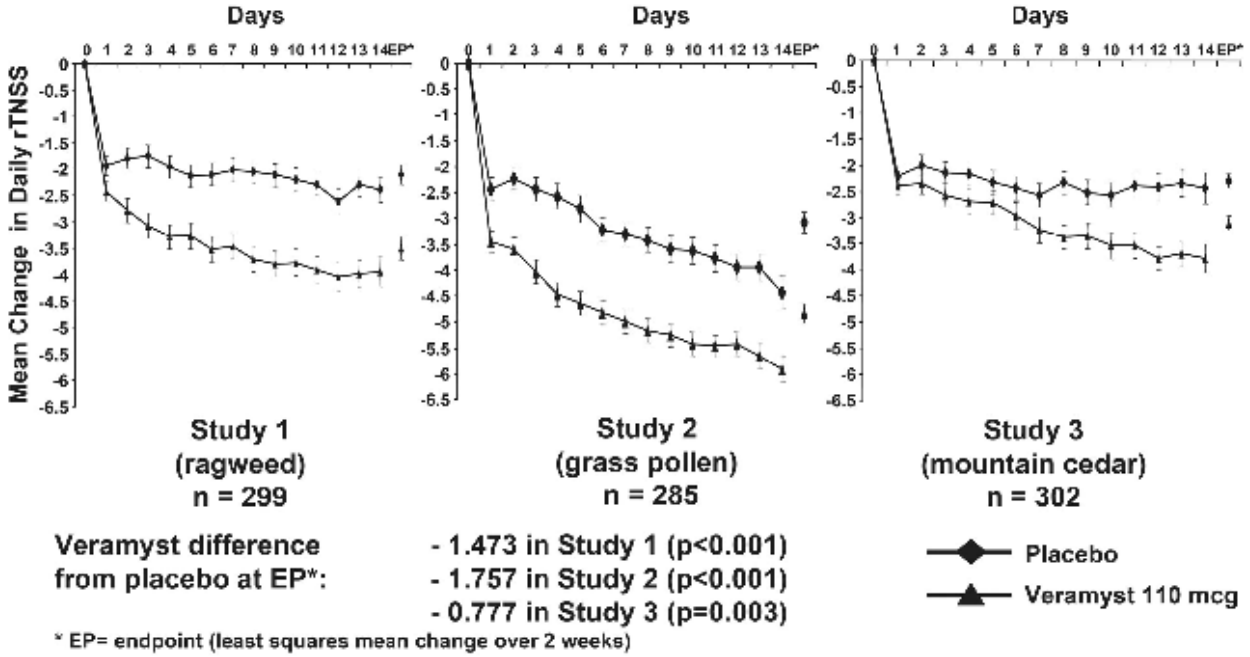


Figure 10. Mean Change from Baseline in Instantaneous Total Nasal Symptom Scores Across 3 Pivotal Studies

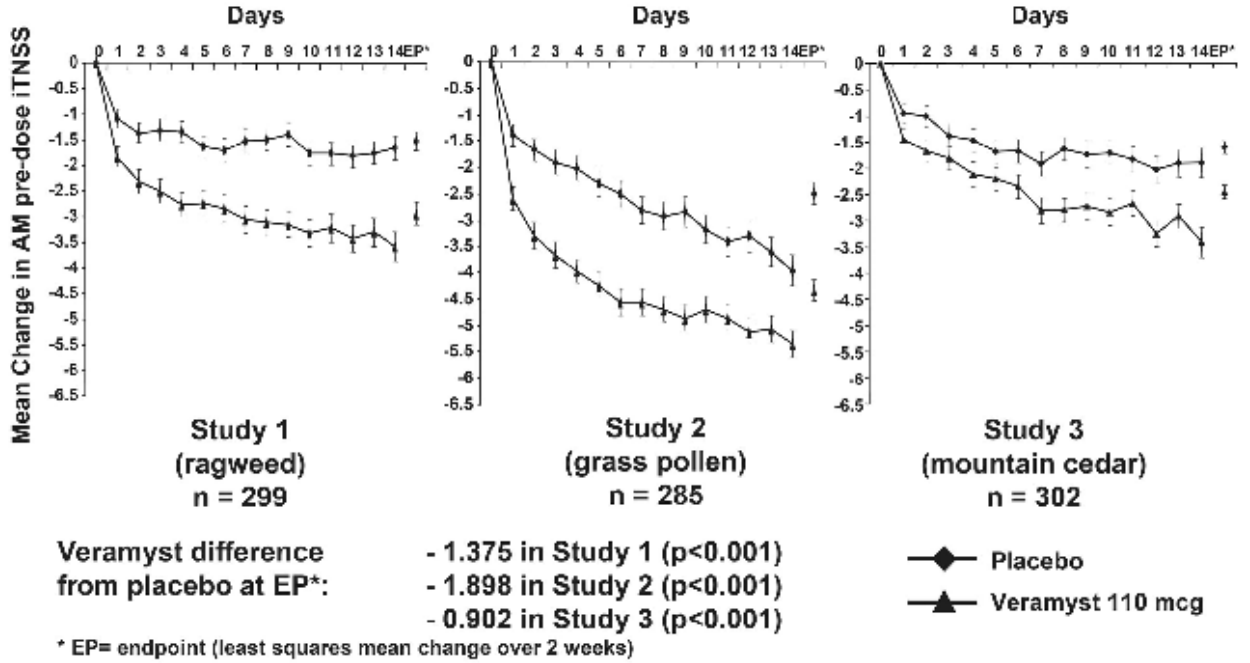


Figure 11. Mean Change from Baseline in Reflective Total Ocular Symptoms Scores Across 3 Pivotal Studies

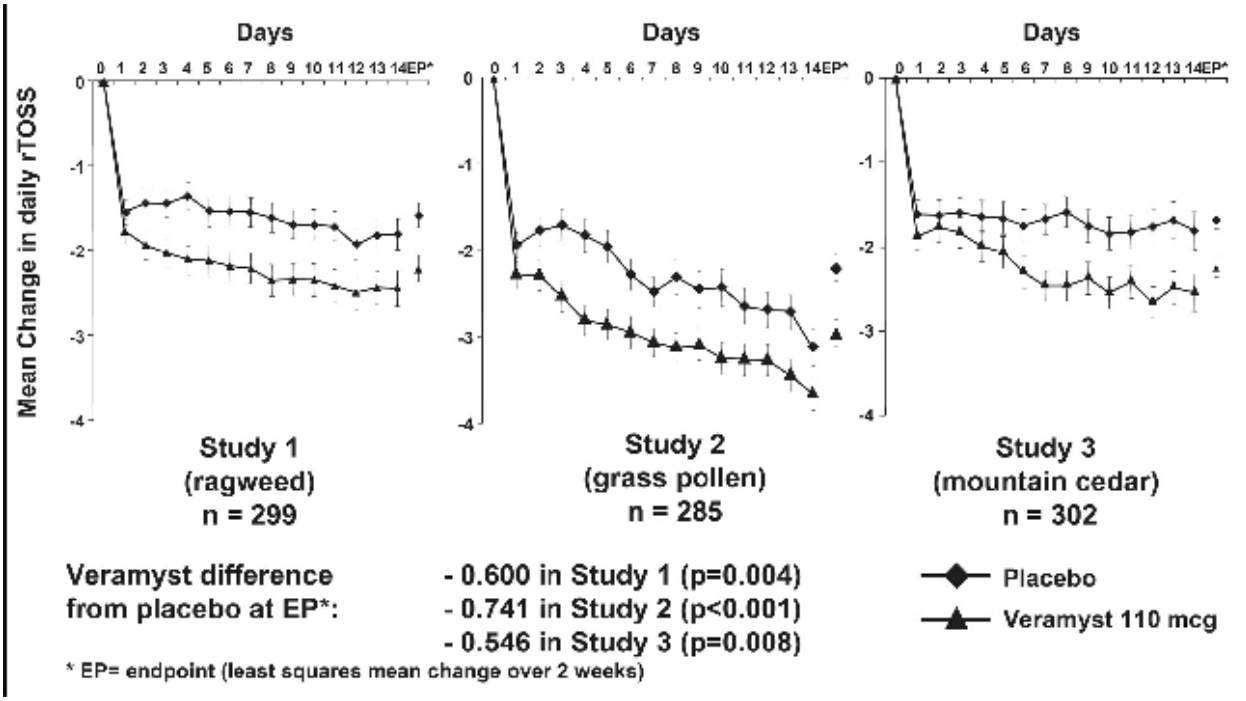
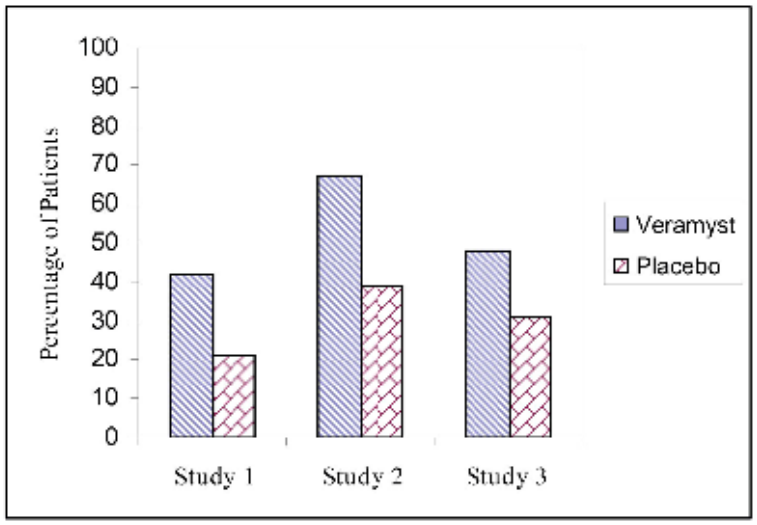


Figure 12. Percentage of Patients Who Rated Their Overall Response to Therapy as 'Significantly' or 'Moderately Improved' (*P* = 0.001 for all comparisons)



Safety

Safety measures included adverse reaction reporting, routine laboratory tests, 12-lead electrocardiograms, vital signs, and nasal examinations. *Veramyst* 110 mcg once daily was well tolerated. In Study 1, 21% of patients in the group receiving *Veramyst* and 12% in the placebo patients reported an adverse reaction. In Studies 2 and 3, there were similar percentages of patients reporting adverse reactions with *Veramyst* (17%, Study 2; 22%, Study 3) compared with placebo (16% and 19%, respectively). In the three studies, the most common adverse reaction in both groups was headache. Headache was reported by 8%, 9%, and 5% of patients receiving *Veramyst* in Studies 1, 2 and 3 respectively, compared with 3%, 6%, and 4% in the placebo patients (Studies 1, 2 , and 3, respectively).

The most common drug-related adverse reaction was epistaxis which occurred in the patients receiving *Veramyst* at incidence rates of 2%, 3%, and 3% (Studies 1, 2, and 3, respectively) compared with <1%,

<1%, and 3% for the placebo patients (Studies 1, 2 , and 3, respectively). All episodes of epistaxis were mild or moderate, with 75% being mild in severity, and only 1 not having resolved by the end of the study period.

Findings from the nasal examinations were generally similar between the treatment groups across the three studies. In Study 1, at Week 2, 4% and <1% of patients receiving *Veramyst* and placebo, respectively had worsened mucosal bleeding. In Study 2, two patients (1%) receiving *Veramyst* and 3 patients (2%) receiving placebo reported nasal ulcers at baseline. At Week 2, 5 patients (4%) of patients receiving *Veramyst* and no patients receiving placebo had nasal ulcers.

The incidence of laboratory abnormalities was low and similar between the treatment groups across all three studies. Changes in vital signs were minor and similar across the treatment groups. There was one patient receiving *Veramyst* who had a clinically significant abnormal ECG findings that was considered not related to the study medication. No other patients treated with *Veramyst* had clinically significant abnormal ECG findings.

5.3 Pivotal Efficacy and Safety Trials with *Veramyst* in Adult and Adolescent Patients with Perennial Allergic Rhinitis

Efficacy and Safety Clinical Trials

The safety and efficacy of *Veramyst* 110 mcg QD in patients with PAR aged ≥12 years was evaluated in 2 multi-center, randomized, double-blind, placebo-controlled, parallel-group clinical trials. Study 1[23,77,21] and Study 2[29,22] were conducted over 4-weeks (N=302) and 6-weeks (N=302), respectively. Patients in both studies were symptomatic to appropriate perennial allergens including animal dander, house dust mites, cockroach, and/or mold and were required to have a rTNSS ≥6 (out of a possible score of 12). Baseline rTNSS scores were 8.6 and 8.7 for Study 1 and Study 2, respectively. Patients were not required to have a predetermined degree of ocular symptomatology prior to randomization.

The primary efficacy measure for both studies was the mean change from baseline over the entire treatment period in daily rTNSS. Key secondary endpoints included mean change from baseline over the entire treatment period in iTNSS and ORT. Other secondary nasal efficacy endpoints included mean change from baseline over entire treatment period in AM rTNSS and PM rTNSS. Ocular efficacy was assessed as a secondary endpoint and included mean change from baseline over the entire treatment period in rTOSS and iTOSS.

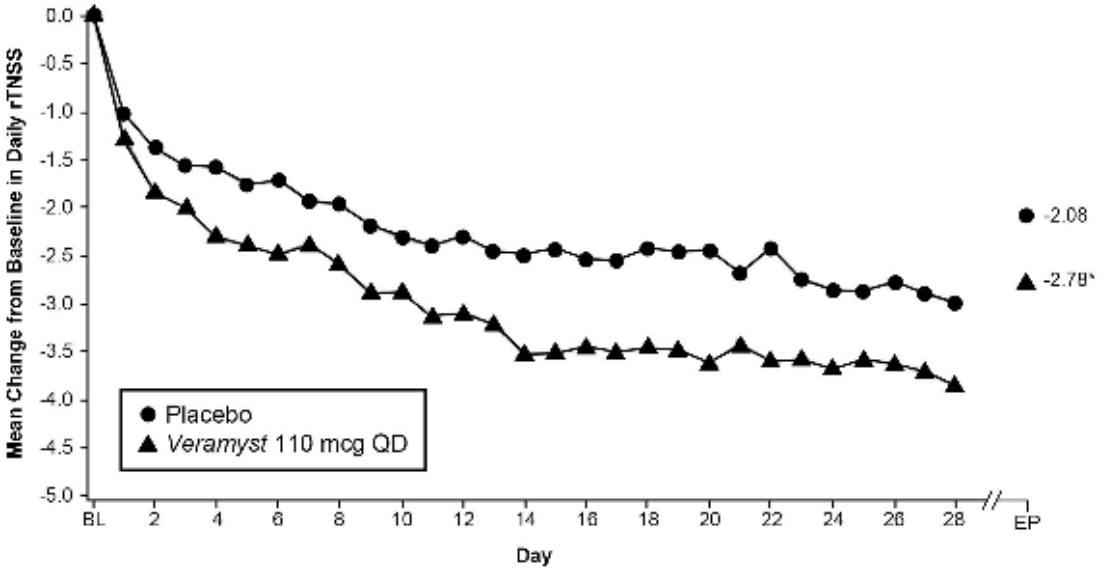
Efficacy

For the primary efficacy endpoint of mean change from baseline over the entire treatment period in daily rTNSS, *Veramyst* was significantly more efficacious in reducing the nasal symptoms of PAR versus vehicle placebo over weeks 1-4 (P=0.005) Figure 13 and over weeks 1-6 (P<0.001) Figure 14. *Veramyst* 110 mcg was also significantly more efficacious than vehicle placebo nasal spray for the 2 key secondary endpoints: mean change from baseline in AM pre-dose iTNSS (Table 8) and the ORT.

In Study 1, the ORT between *Veramyst* and placebo was statistically significant (P=0.005) with 44% of patients treated with *Veramyst* reported significant or moderate improvement compared with 33% of placebo-treated patients. Likewise in Study 2, the difference between *Veramyst* and placebo was statistically significant (P<0.001) with significant or moderate improvement ratings reported in 62% and 39% of patients treated with *Veramyst* and placebo, respectively.

For the secondary endpoint (daily rTOSS), a significant difference between *Veramyst* 110 mcg and vehicle placebo was not observed over the treatment period of 4 weeks in Study 1 (P=0.428) but was demonstrated over 6 weeks in Study 2 (P=0.004) (Table 8).

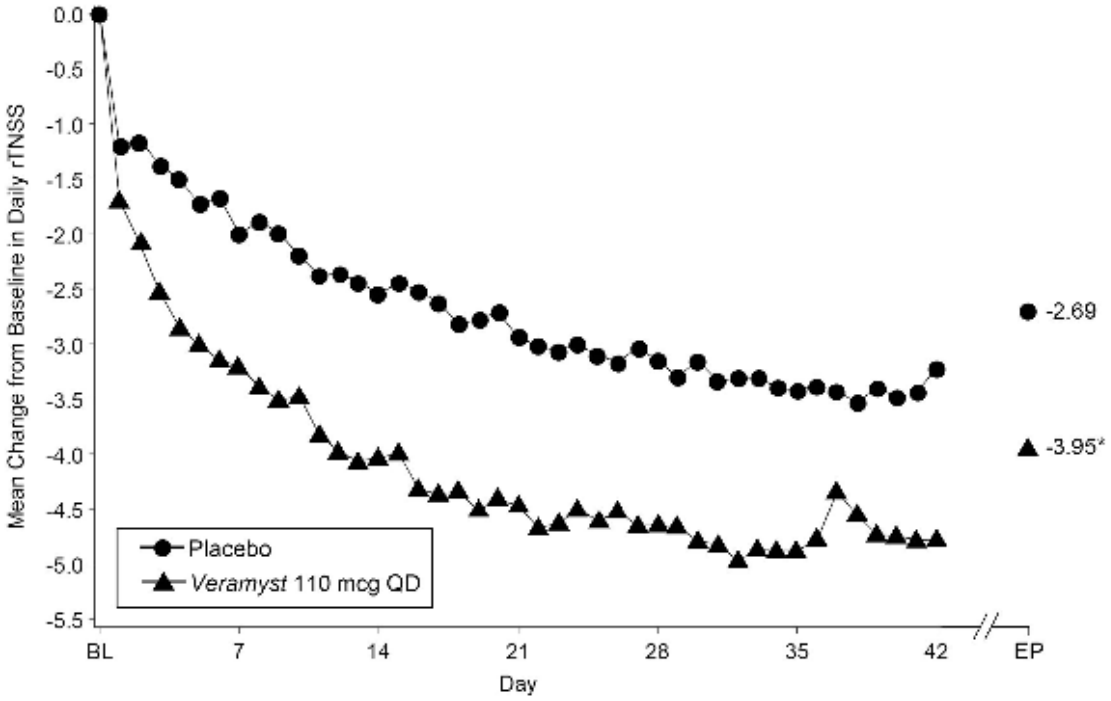
Figure 13. Mean Change from Baseline in Daily rTNSS over 4-Week Treatment Period (Study 1)



EP=endpoint (least square mean change over 4 weeks)

*P=0.005 vs placebo

Figure 14. Mean Change from Baseline in Daily rTNSS over 6-week Treatment Period (Study 2)



EP=endpoint (least square mean change over 6 weeks)

*P<0.001 vs placebo

Table 8. Change from Baseline in Primary and Secondary Endpoints from Studies in Adult and Adolescent Patients with Perennial Allergic Rhinitis

Study 1 (Weeks 1-4)* **Study 2 (Weeks 1-6)***	**Vehicle Placebo** (n=153) (n=151)	***Veramyst* 110 mcg QD** (n=149) (n=151)		
Endpoint	**LS Mean Change**	**LS Mean Change**	**LS Difference (95% CI)**	***P*- value**
Daily rTNSS†				
Study 1	-2.08	-2.78	-0.71 (-1.20, -0.21)	0.005
Study 2	-2.69	-3.95	-1.26 (-1.73, -0.78)	<0.001
AM pre-dose iTNSS‡				
Study 1	-1.75	-2.45	-0.71 (-1.20, -0.21)	0.006
Study 2	-2.36	-3.82	-1.5 (-1.93, -0.99)	<0.001
AM rTNSS§				
Study 1	-2.07	-2.81	-0.74 (-1.24, -0.23)	0.004
Study 2	-2.66	-3.93	-1.27 (-1.74, -0.81)	<0.001
PM rTNSS§				
Study 1	-2.10	-2.76	-0.66 (-1.17, -0.16)	0.011
Study 2	-2.73	-4.02	-1.29 (-1.77, -0.81)	<0.001
Daily rTOSS§				
Study 1	-1.24	-1.39	-0.15 (-0.52, 0.22)	0.428
Study 2	-1.41	-1.92	-0.51 (-0.85, -0.16)	0.004
AM pre-dose iTOSS§				
Study 1	-1.14	-1.38	-0.24 (-0.63, 0.15)	0.228
Study 2	-1.26	-1.76	-0.49 (-0.85, -0.13)	0.007

KEY: LS=Least Square; CI=Confidence Interval

*entire treatment period

†primary efficacy endpoint

‡key secondary endpoint

§other secondary endpoints

Safety

Veramyst 110 mcg QD was generally well-tolerated. In the 4-week[77] and 6-week[29] clinical trials, no safety issues were identified from vital signs, electrocardiogram assessments, and laboratory values. Table 9 displays the common drug-related adverse reactions with an incidence of >1%. The most common drug-related adverse event, epistaxis, was reported in 8% of patients treated with *Veramyst* and 4-5% of placebo-treated patients. The majority of cases of epistaxis in both treatment groups were of mild intensity.

Table 9. Adverse Reactions with >1% Incidence in Controlled Clinical Trials in Adult and Adolescent Patients 12 Years of Age and Older with Perennial Allergic Rhinitis

	Study 1 (4-Week Trial)	
Adverse Event	**Placebo (n=153)** **n (%)**	***Veramyst* 110 mcg (n=149)** **n (%)**
Patients with any drug-related event	20 (13)	29 (19)
Epistaxis	8 (5)	12 (8)
Headache	6 (4)	7 (5)
Nasal septum ulceration	2 (1)	6 (4)
Nasal ulcer	1 (<1)	3 (2)

	Study 2 (6-Week Trial)	
	Placebo (n=151) **n (%)**	***Veramyst* 110 mcg (n=151)** **n (%)**
Patients with any drug-related event	17 (11)	22 (15)
Epistaxis	6 (4)	12 (8)
Headache	3 (2)	2 (1)
Nasal septum ulceration	0	4 (3)

5.4 Pivotal Efficacy and Safety Trials with *Veramyst* in Pediatric Patients with Seasonal Allergic Rhinitis

Pivotal Efficacy and Safety Trial

The safety and efficacy of *Veramyst* was evaluated in a 2-week, double-blind, placebo-controlled, U.S. trial.[26,80] A total of 554 pediatric patients 2 to <12 years of age with a diagnosis of SAR symptomatic to pollen were randomized to receive *Veramyst* 55 mcg, 110 mcg, or vehicle placebo nasal spray QD in the morning. The primary efficacy endpoint was the mean change from baseline over the entire treatment period in the daily rTNSS using an intent-to-treat (ITT) analysis in patients 6 to <12 years old and supported by an analysis of the entire ITT population in 2 to 11 year old patients. Key secondary endpoints included the mean change from baseline over the entire treatment period in the AM iTNSS and the ORT.

Ocular efficacy was assessed with secondary endpoints that included mean change from baseline over the entire treatment period in the morning, evening and daily rTOSS.

Results

All 554 patients randomized into the study received at least one dose of study medication and were included in the analyses; 448 and 105 patients were 6 to <12 and 2 to <6 years of age, respectively.[80] One patient was withdrawn from the study on Day 8 due to an age protocol violation; however was included in the entire ITT population of children 2 to 11 years of age.

For the primary efficacy endpoint of mean change from baseline over the entire treatment period in daily rTNSS for patients 6 to <12 years old, *Veramyst* 110 mcg was significantly more efficacious ($P = 0.025$) in reducing the nasal symptoms of SAR versus vehicle placebo (Figure 15 and Table 10). However, there was no difference between *Veramyst* 55 mcg and placebo for the primary endpoint.

Daily rTNSS analyses performed with a population that included patients ages 2 to <12 years, showed similar results for *Veramyst* 110 mcg versus placebo [least squared (LS) mean difference = -0.609; $P = 0.012$].[26]

Figure 15. Mean Change from Baseline in Daily rTNSS for Patients Aged 6 to <12 Years with Seasonal Allergic Rhinitis - Intent to Treat Analysis[80]

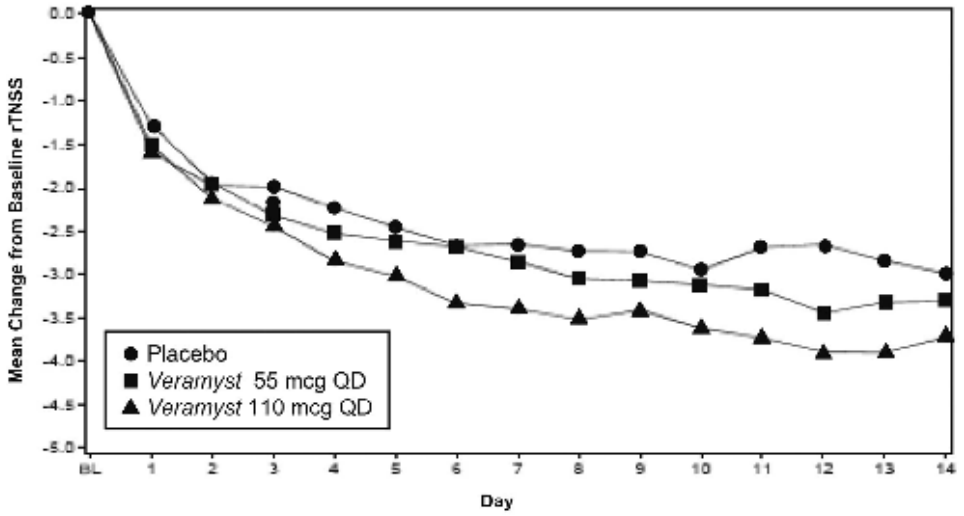


Table 10. Mean Change from Baseline in Primary and Secondary Efficacy Outcomes in Patients 6 to <12 Years of Age with Seasonal Allergic Rhinitis - Intent-to-Treat Analysis[23]

Treatment	n	Baseline	Change from Baseline – LS Mean	Difference from Placebo		
				LS Mean	95% CI	*P*-value
Reflective Total Nasal Symptom Scores						
Veramyst 55 mcg	151	8.6	-2.71	-0.161	-0.69, 0.37	0.553
Veramyst 110 mcg	146	8.5	-3.16	-0.62	-1.15, -0.08	0.025
Vehicle Placebo	149	8.4	-2.54	-	-	-
Instantaneous Total Nasal Symptom Scores						
Veramyst 55 mcg	151	8.4	-2.37	-0.234	-0.77, 0.30	0.389
Veramyst 110 mcg	146	8.3	-2.80	-0.67	-1.21, -0.13	0.015
Vehicle Placebo	149	8.4	-2.13	-	-	-

Reflective total nasal symptom score = average of daytime and nighttime TNSS evaluated over 12 hour intervals; **Instantaneous total nasal symptom score** = score at the end of the 24-hour dosing interval performed at the moment immediately prior to taking the daily dose; **CI** = confidence interval; **LS** = least square

Veramyst 110 mcg was significantly more efficacious than vehicle placebo for the secondary endpoints morning pre-dose iTNSS and ORT for children 6 to <12 years old (Table 10 and Table 11). A total of 62% of patients receiving *Veramyst* 110 mcg reported significant or moderate improvement at the end of the study compared with 43% of patients receiving placebo. *Veramyst* 55 mcg did not demonstrate a significantly greater change from baseline compared with vehicle placebo for either of these secondary endpoints.

Veramyst 110 mcg also demonstrated significantly greater improvements in morning pre-dose iTNSS and ORT for the entire study population of children 2 to <12 years old ($P = 0.008$ and $P < 0.001$; respectively).[80]

Table 11. Change from Baseline in Overall Response to Therapy in Children 6 to <12 Years of Age with Seasonal Allergic Rhinitis - Intent-to-Treat Analysis[80]

Endpoint	Vehicle Placebo (n = 150)	*Veramyst* 55 mcg (n = 152)	*Veramyst* 110 mcg (n = 146)
Significantly Improved	13%	20%	28%
Moderately Improved	30%	26%	34%
Mildly Improved	23%	31%	26%
No Change	27%	17%	10%
Mildly Worse	3%	1%	0
Moderately Worse	1%	3%	0
Significantly Worse	2%	<1%	1%
P-value vs. placebo	-	0.083	<0.001

A significant difference between the study treatments was not observed for the ocular endpoints.[80] However, ocular symptoms were only mild at baseline.

Safety

Safety measures included adverse reaction reporting, routine laboratory tests, 12-lead electrocardiograms (ECGs), vital signs, and nasal examinations.[80] *Veramyst* 55 mcg and 110 mcg QD were generally well-tolerated. During the 2-week treatment period, 30% of both groups receiving *Veramyst* and 20% of the group receiving placebo reported adverse reactions. The most common adverse event was headache. This was the only adverse event which occurred at an incidence >3% and occurred more commonly with active drug than placebo. The incidence of headache was 4% for patients treated with *Veramyst* 55 mcg, 6% for *Veramyst* 110 mcg, and 4% for placebo.

The number of drug-related adverse reactions was similar among treatment groups (placebo and *Veramyst* 110 mcg - 5%, *Veramyst* 55 mcg - 6%). The most common drug-related adverse reaction was epistaxis which occurred in 2% of patients treated with placebo and *Veramyst* 110 mcg and 3% of patients treated with *Veramyst* 55 mcg. All episodes of epistaxis were mild or moderate, with 77% being mild in severity. Four patients from the placebo group, 4 from the group receiving *Veramyst* 55 mcg, and 2 patients receiving *Veramyst* 110 mcg withdrew from the study due to an adverse reaction.

The incidence of laboratory abnormalities was low and similar between the 3 treatment groups. Findings from the nasal examinations were similar across the 3 treatment groups. Changes in vital signs were minor and similar across the treatment groups. There were no clinically significant abnormal ECG findings for any patient.

5.5 Pivotal Efficacy and Safety Trials with *Veramyst* in Pediatric Patients with Perennial Allergic Rhinitis

Pivotal Efficacy and Safety Trial

The safety and efficacy of *Veramyst* were evaluated in a 12-week, double-blind, placebo-controlled, international trial.[79,81] A total of 558 patients aged 2 to <12 years with a diagnosis of PAR symptomatic to a perennial allergen (e.g., animal dander, house dust mites, cockroach, or mold) were randomized to receive *Veramyst* 55 mcg, 110 mcg, or vehicle placebo nasal spray daily (QD) in the morning. Patients could not have had significant concomitant medical conditions or be using corticosteroids, allergy medications, or other medications concurrently that could affect allergic rhinitis or its symptoms. Patients who also had a history of allergy to a seasonal pollen that would be present in their geographic area during study participation were not eligible.

The primary efficacy measure for the study was the mean change from baseline over the first 4 weeks of treatment in daily rTNSS using a reduced intent-to-treat (RITT) population in patients 6 to <12 years of age and supported by similar analyses in the entire RITT population of patients 2 to <12 years of age. The RITT population excluded patients from one site due to study conduct irregularities. Key secondary measures in the RITT population were the mean change from baseline over the first 4 weeks of treatment in morning, pre-dose iTNSS and an overall evaluation of response to therapy. Ocular efficacy was not assessed in this trial.

Results

All 558 patients randomized into the study received at least one dose of study medication and comprised an intent-to-treat (ITT) population for evaluating safety.[79] The RITT population (N = 550) included patients 2 to <6 years of age (n = 115), 6 to <12 years of age (n = 431), and 4 patients ≥12 years of age.

For the primary efficacy endpoint of mean change from baseline over the first 4 weeks of the treatment in the daily rTNSS in the RITT population of patients 6 to <12 years of age, *Veramyst* 55 mcg significantly reduced daily rTNSS (Figure 16 and Table 12). *Veramyst* 110 mcg QD reduced daily rTNSS compared with vehicle placebo but the difference was not statistically significant. For analysis of the primary endpoint using the entire RITT population which included patients 2 to <12 years of age, *Veramyst* 110 mcg and 55 mcg both significantly reduced daily rTNSS compared with vehicle placebo [least squared (LS) mean difference = -0.475, $P = 0.031$ for 110 mcg; LS mean difference = -0.812, $P < 0.001$ for 55 mcg].

Figure 16. Mean Change from Baseline in Daily rTNSS Over the First 4 Weeks of Treatment in Patients 6 to <12 Years - Reduced Intent-to-Treat Population[79]

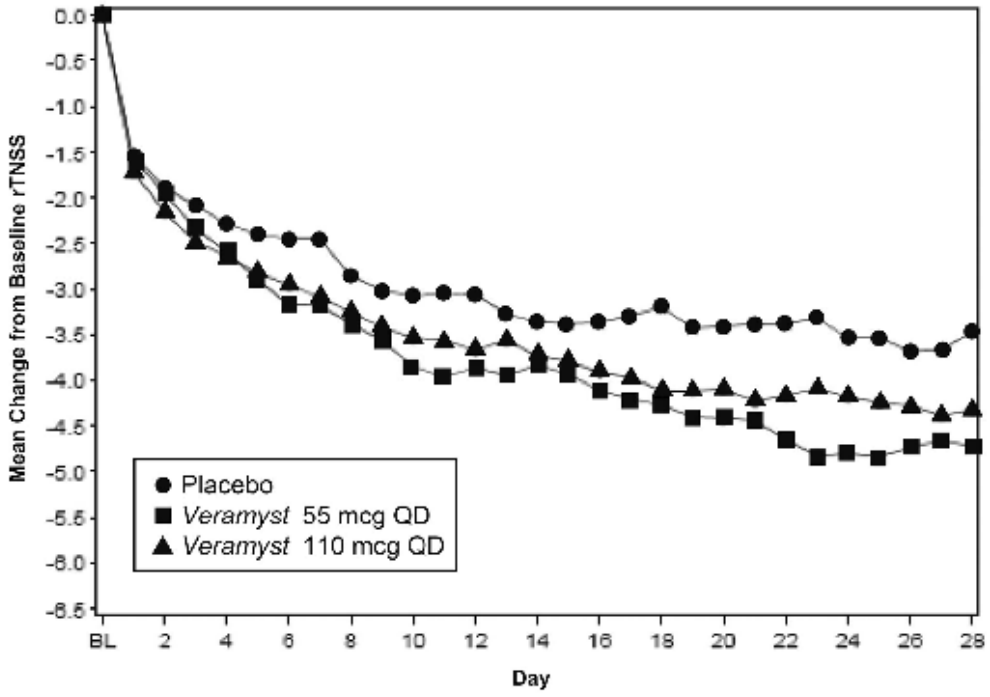


Table 12. Mean Change from Baseline in Primary and Secondary Efficacy Outcomes in Patients 6 to <12 Years of Age with Perennial Allergic Rhinitis - Reduced Intent-to-Treat Population[23]

Treatment	n	Baseline	Change from Baseline – LS Mean	Difference from Placebo		
				LS Mean	95% CI	*P*-value
Reflective Total Nasal Symptom Scores						
Veramyst 55 mcg	144	8.5	-4.16	-0.75	-1.24, -0.27	0.003
Veramyst 110 mcg	140	8.6	-3.86	-0.452	-0.95, 0.04	0.073
Vehicle Placebo	147	8.5	-3.41	-	-	-
Instantaneous Total Nasal Symptom Scores						
Veramyst 55 mcg	144	8.3	-3.62	-0.751	-1.24, -0.27	0.002
Veramyst 110 mcg	140	8.3	-3.52	-0.651	-1.14, -0.16	0.009
Vehicle Placebo	147	8.3	-2.87	-	-	-
Reflective total nasal symptoms score = average of daytime and nighttime TNSS evaluated over 12 hour intervals; **Instantaneous total nasal symptoms score** = score at the end of the 24-hour dosing interval performed at the moment immediately prior to taking the daily dose; **CI** = confidence interval; **LS** = least square						

Veramyst 55 mcg and 110 mcg demonstrated a significantly greater reduction from baseline in morning pre-dose iTNSS compared with placebo (Table 12). For the secondary endpoint ORT, only *Veramyst* 55 mcg was significantly different from placebo (Table 13).

Table 13. Change from Baseline in Overall Response to Therapy in Children 6 to < 12 Years of Age with Perennial Allergic Rhinitis - Reduced Intent-to-Treat Population[79]

Efficacy Endpoint	Vehicle Placebo (n = 147)	*Veramyst* 55 mcg QD (n = 144)	*Veramyst* 110 mcg QD (n = 140)
Significantly Improved	27 (20)	40 (31)	33 (26)
Moderately Improved	55 (40)	46 (36)	41 (32)
Mildly Improved	31 (22)	29 (23)	36 (28)
No Change	18 (13)	12 (9)	15 (12)
Mildly Worse	3 (2)	0	1 (<1)
Moderately Worse	3 (2)	0	1 (<1)
Significantly Worse	1 (<1)	1 (<1)	0
P value vs. placebo	----	0.024	<0.414

The LS mean differences between *Veramyst* 110 mcg and placebo for the individual nasal symptom reflective ratings were: nasal congestion (-0.189; $P = 0.011$), rhinorrhea (-0.108; $P = 0.132$), nasal itching (-0.076; $P = 0.286$, and sneezing (-0.089; $P = 0.211$).[79] The LS mean differences between *Veramyst* 110 mcg and placebo for morning predose instantaneous assessments of all individual nasal symptoms were: nasal congestion (-0.239; $P = 0.001$), rhinorrhea (-0.145; $P = 0.047$), nasal itching (-0.122; $P = 0.085$), and sneezing (-0.157; $P = 0.035$).

The LS mean differences between *Veramyst* 55 mcg and placebo for the individual nasal symptom reflective ratings were: rhinorrhea (-0.175; $P = 0.014$), nasal congestion (-0.230; $P = 0.002$), nasal itching (-0.160; $P = 0.024$), and sneezing (-0.190; $P = 0.007$). The LS mean differences between *Veramyst* 55 mcg and placebo for the morning instantaneous ratings were: rhinorrhea (-0.182; $P = 0.012$), nasal congestion (-0.214; $P = 0.003$), nasal itching (-0.179; $P = 0.011$), and sneezing (-0.177; $P = 0.016$).

Safety

All 558 patients randomized into the study received at least one dose of study medication and were included in the evaluation of safety.[79] *Veramyst* 55 mcg and 110 mcg QD were well tolerated. During the treatment period, adverse reactions occurred in 59%, 56%, and 59% of patients receiving placebo, *Veramyst* 55 mcg, and *Veramyst* 110 mcg, respectively. Pharyngolaryngeal pain was the most common adverse reaction that occurred at an incidence >3%. The incidence of pharyngolaryngeal pain was 7%, 7%, and 5% in patients receiving placebo, *Veramyst* 55 mcg and *Veramyst* 110 mcg, respectively.

The number of drug-related adverse reactions was similar among treatment groups (placebo-11%, *Veramyst* 55 mcg-12%, and *Veramyst* 110 mcg-9%). The most common drug-related adverse reaction

was epistaxis (placebo and *Veramyst* 55 mcg-4%, *Veramyst* 110 mcg-3%). All episodes of epistaxis were mild or moderate, with 86% being mild in severity.

Eight patients in the placebo group, 6 patients receiving *Veramyst* 55 mcg and 2 subjects receiving *Veramyst* 110 mcg withdrew due to an adverse reaction. One patient in each of the groups receiving *Veramyst* 55 mcg and 110 mcg withdrew due to a drug-related reaction (nasal candidiasis and nostril mycosis, respectively). Three subjects in the placebo group withdrew due to a drug-related adverse reaction (subcapsular cataract, headache and epistaxis).

None of the patients in either the active treatments or placebo groups had 24-hour urinary cortisol (UC) excretion below the normal range at baseline or at study endpoint. Decreases from baseline were observed in 24-hour UC excretion for both groups receiving *Veramyst* compared with placebo; however, neither was considered clinically relevant. The incidence of laboratory abnormalities was low and similar between the 3 treatment groups.

Findings from the nasal examinations were similar across the 3 treatment groups. One patient in each of the groups receiving *Veramyst* had a positive culture for candidiasis during treatment. The patient receiving *Veramyst* 55 mcg was withdrawn because of this adverse reaction, which was considered drug-related. Changes in vital signs were minor and similar across the 3 treatment groups. One patient each in the groups receiving placebo and *Veramyst* 55 mcg had a clinically significant abnormal electrocardiogram (ECG), prolonged QTc interval, at endpoint. The reaction was considered drug-related in the patient receiving *Veramyst* 55 mcg.

Slit lamp, lens, and conjunctival examinations showed corneal and lens changes in ≤2% of patients across treatment groups. Four patients receiving *Veramyst* 55 mcg reported a cataract in at least 1 eye, compared with 2 patients in the placebo group. None of the patients receiving *Veramyst* 110 mcg developed a cataract during the study. From the ophthalmic assessments in this study, *Veramyst* 55 mcg or 110 mcg QD for 12 weeks did not increase the risk of an adverse treatment effect on the eyes compared with placebo.

5.6 Efficacy Trials of *Veramyst* in Treating Ocular Symptoms of Allergic Rhinitis

Background for Ocular Assessments

Ocular symptoms (itching/burning, tearing/watering, and redness) were assessed during clinical trials with *Veramyst* and were based on patient- or parent/guardian-rated, individual symptom assessments as evaluated on a 4-point (0 to 3) categorical severity scale (0 = absent, 1 = mild, 2 = moderate, 3 = severe) and recorded on diary cards.[23] Ocular efficacy of *Veramyst* was assessed by the mean change from baseline over the entire treatment period in daily reflective, total ocular symptom scores (rTOSS), a secondary study endpoint. The total ocular symptom score (TOSS) is the sum of 3 individual symptom scores for eye itching/burning, eye tearing/watering, and eye redness. The rTOSS is a rating of the severity of symptoms over the previous 12 hours and was performed in the morning (AM rTOSS) and evening (PM rTOSS). The daily rTOSS is the average of the AM rTOSS and PM rTOSS assessments.

Other secondary ocular efficacy endpoints included mean change from baseline over the entire treatment period in AM and PM rTOSS and AM pre-dose instantaneous TOSS (iTOSS), i.e. the ocular symptom score at the end of the 24-hour dosing interval, immediately prior to the next dose. Individual AM, PM, rTOSS, and AM iTOSS scores for itching/burning, tearing/watering, and redness were also assessed.[18] Mean percent change from baseline over the entire treatment period in daily rTOSS and AM pre-dose iTOSS were also evaluated in studies in adults and adolescent patients with seasonal allergic rhinitis (SAR).

Seasonal Allergic Rhinitis

Adults and Adolescents Aged 12 Years and Older

The safety and efficacy of *Veramyst* 110 mcg QD in patients aged ≥12 years was evaluated in 3, 2-week, multi-center, randomized, double-blind, placebo-controlled, parallel-group clinical trials. Studies 1 (N=299)[73,18], 2 (N=285)[75,20], and 3 (N=302)[76,82] consisted of patients diagnosed with SAR due to ragweed, grass pollen, and mountain cedar, respectively. Patients were randomized to 2 weeks' treatment with intranasal *Veramyst* 110 mcg or vehicle placebo QD in the morning. Prior to randomization, patients were required to have an rTOSS value of ≥4.

The ocular efficacy endpoint was the mean change from baseline over the entire treatment period in daily rTOSS (Figure 11). Overall, rTOSS values at baseline were 6.5, 5.4, and 6.6 for Study 1, 2 and 3, respectively. For this key secondary study endpoint, *Veramyst* 110 mcg QD was significantly ($P < 0.01$) more efficacious in reducing the ocular symptoms of SAR versus vehicle placebo in all 3 studies.

A significant difference in favor of *Veramyst* was also seen for most other secondary ocular endpoints (Table 14), including individual ocular symptoms (Table 2). In Study 3, percent change in AM pre-dose iTOSS (Table 14), individual symptom of eye tearing/watering for the AM pre-dose instantaneous (Table 15) and individual symptom of eye tearing/watering for PM reflective results (Table 15) did not reach statistical significance.

Table 14. Change from Baseline in Other Secondary Ocular Efficacy Endpoints from Studies in Adult and Adolescent Patients with Seasonal Allergic Rhinitis

Weeks 1-2*	**Vehicle Placebo**	***Veramyst* 110 mcg QD**		
Study 1 (Ragweed)	**(n=148)**	**(n=151)**		
Study 2 (Grass)	**(n=144)**	**(n=141)**		
Study 3 (Mt Cedar)	**(n=150)**	**(n=152)**		
Endpoint	**LS Mean Change**	**LS Mean Change**	**LS Difference (95% CI)**	***P*-value**
AM pre-dose iTOSS				
Study 1	-1.30	-1.86	-0.553 (-0.95, -0.15)	0.007
Study 2	-1.84	-2.61	-0.764 (-1.17, -0.35)	<0.001
Study 3	-1.05	-1.57	-0.519 (-0.91, -0.13)	0.009
AM rTOSS				
Study 1	-1.58	-2.15	-0.572 (-0.98, -0.16)	0.007
Study 2	-2.12	-2.91	-0.785 (-1.19, -0.38)	<0.001
Study 3	-1.49	-1.99	-0.498 (-0.90, -0.09)	0.016
PM rTOSS				
Study 1	-1.70	-2.35	-0.65 (-1.08, -0.22)	0.003
Study 2	-2.39	-3.08	-0.696 (-1.11, -0.29)	<0.001
Study 3	-1.73	-2.27	-0.539 (-0.97, -0.11)	0.014
% Change Daily rTOSS				
Study 1	-25.37	-34.21	-8.831 (-15.3, -2.33)	0.008
Study 2	-42.08	-56.07	-13.996 (-22.0, -6.02)	<0.001
Study 3	-23.68	-32.46	-8.779 (-15.1, -2.49)	0.006
% Change AM pre-dose iTOSS				
Study 1	-19.86	-28.49	-8.626 (-15.3, -1.91)	0.012
Study 2	-33.62	-49.62	-16.002 (-24.9, -7.14)	<0.001
Study 3	-16.53	-23.93	-7.407 (-15.0, 0.15)	0.055
KEY: LS=Least Square; CI=Confidence Interval				
*=entire treatment period				

Table 15. Change from Baseline in Individual Ocular Symptom Endpoints from Studies in Adult and Adolescent Patients with Seasonal Allergic Rhinitis

Weeks 1-2*	**Vehicle Placebo**	***Veramyst* 110 mcg QD**		
Study 1 (Ragweed)	**(n=148)**	**(n=151)**		
Study 2 (Grass)	**(n=144)**	**(n=141)**		
Study 3 (Mt Cedar)	**(n=150)**	**(n=152)**		
Endpoint	**LS Mean Change**	**LS Mean Change**	**LS Difference (95% CI)**	***P*-value**
Daily Reflective Individual Symptom Score				
Eye Itching/Burning				
Study 1	-0.59	-0.74	-0.159 (-0.30, -0.01)	0.033
Study 2	-0.79	-1.04	-0.258 (-0.40, -0.11)	<0.001
Study 3	-0.51	-0.70	-0.195 (-0.34, -0.05)	0.007
Eye Tearing/Watering				
Study 1	-0.54	-0.79	-0.247 (-0.39, -0.10)	0.001
Study 2	-0.75	-0.99	-0.245 (-0.38, -0.11)	<0.001
Study 3	-0.60	-0.76	-0.157 (-0.30, -0.01)	0.032
Eye Redness				
Study 1	-0.51	-0.70	-0.190 (-0.34, -0.04)	0.013
Study 2	-0.73	-0.96	-0.238 (-0.38, -0.10)	<0.001
Study 3	-0.49	-0.69	-0.198 (-0.34, -0.06)	0.006
AM pre-dose Instantaneous Individual Symptom Score				
Eye Itching/Burning				
Study 1	-0.49	-0.64	-0.151 (-0.30, -0.00)	-0.044
Study 2	-0.64	-0.89	-0.259 (-0.41. -0.11)	<0.001
Study 3	-0.35	-0.55	-0.195 (-0.33, -0.05)	0.007
Eye Tearing/Watering				
Study 1	-0.43	-0.64	-0.206 (-0.36, -0.06)	0.007
Study 2	-0.60	-0.85	-0.250 (-0.39, -0.11)	<0.001
Study 3	-0.40	-0.53	-0.138 (-0.28, 0.01)	0.065
Eye Redness				
Study 1	-0.38	-0.57	-0.186 (-0.33, -0.04)	0.012
Study 2	-0.61	-0.86	-0.257 (-0.40, -0.11)	<0.001
Study 3	-0.30	-0.50	-0.203 (-0.34, -0.07)	0.004
AM Reflective Individual Symptom Scores				
Eye Itching/Burning				
Study 1	-0.58	-0.74	-0.157 (-0.31, -0.01)	0.041
Study 2	-0.73	-1.01	-0.280 (-0.43, -0.13)	<0.001
Study 3	-0.47	-0.66	-0.191 (-0.33, -0.05)	0.009
Eye Tearing/Watering				
Study 1	-0.51	-0.75	-0.232 (-0.38, -0.08)	0.002
Study 2	-0.69	-0.96	-0.265 (-0.40, -0.13)	<0.001
Study 3	-0.54	-0.69	-0.149 (-0.29, 0.00)	0.045

KEY: LS=Least Square; CI=Confidence Interval

*=entire treatment period

Weeks 1-2* **Study 1 (Ragweed)** **Study 2 (Grass)** **Study 3 (Mt Cedar)**	**Vehicle Placebo** **(n=148)** **(n=144)** **(n=150)**	***Veramyst* 110 mcg QD** **(n=151)** **(n=141)** **(n=152)**		
Endpoint	**LS Mean Change**	**LS Mean Change**	**LS Difference (95% CI)**	***P*-value**
Eye Redness				
Study 1	-0.50	-0.67	-0.179 (-0.33, -0.03)	0.021
Study 2	-0.70	-0.94	-0.241 (-0.39, -0.10)	0.001
Study 3	-0.48	-0.64	-0.161 (-0.30, -0.02)	0.027
PM Reflective Individual Symptom Scores				
Eye Itching/Burning				
Study 1	-0.59	-0.77	-0.179 (-0.33, -0.03)	0.021
Study 2	-0.83	-1.07	-0.238 (-0.38, -0.09)	0.002
Study 3	-0.55	-0.73	-0.180 (-0.33, -0.03)	0.019
Eye Tearing/Watering				
Study 1	-0.58	-0.84	-0.263 (-0.42, -0.11)	0.001
Study 2	-0.80	-1.02	-0.221 (-0.36, -0.08)	0.002
Study 3	-0.66	-0.81	-0.151 (-0.30, 0.00)	0.054
Eye Redness				
Study 1	-0.53	-0.74	-0.206 (-0.36, -0.05)	0.009
Study 2	-0.76	-0.99	-0.232 (-0.38, -0.08)	0.002
Study 3	-0.51	-0.72	-0.212 (-0.36, -0.06)	0.006
KEY: LS=Least Square; CI=Confidence Interval *=entire treatment period				

Children Aged 2 to 11 Years

The ocular safety and efficacy of *Veramyst* was evaluated in children aged 2 to 11 years (N= 554) in a 2-week placebo-controlled clinical trial.[78] Patients with SAR symptomatic to pollen were randomized to receive *Veramyst* 55 mcg, 110 mcg, or vehicle placebo nasal spray once daily. All analyses of efficacy data were conducted for the Intent-to-Treat (ITT) subgroup of patients aged 6 to <12 years (N=448), the group of primary interest. There was no significant difference between either dosage of *Veramyst* and intranasal vehicle placebo spray for any secondary study endpoints for ocular efficacy to include daily rTOSS, AM pre-dose iTOSS, and AM or PM rTOSS. Likewise, no significance difference between treatments was observed for any individual ocular symptom scores for AM, PM, or daily reflective scores for ocular itching/burning, tearing/watering, and redness.

Perennial Allergic Rhinitis (PAR)

Adults and Adolescents Aged 12 Years and Older

The effect of *Veramyst* 110 mcg QD on ocular symptoms in patients with PAR aged ≥ 12 years was evaluated in 2 multi-center, randomized, double-blind, placebo-controlled, parallel-group clinical trials. Study 1 and Study 2 were conducted over 4-weeks (N=302)[23] [77] and 6-weeks (N=302),[29,22] respectively. Patients in both studies were symptomatic to appropriate perennial allergens including animal dander, house dust mites, cockroach, and/or mold but were not required to have a predetermined degree of ocular symptomatology prior to randomization.

The ocular efficacy endpoint was the mean change from baseline over the entire treatment periods of 4 or 6 weeks in daily rTOSS. Overall, rTOSS values at baseline were 4.9 and 4.4 for Study 1 and 2, respectively. In the 4-week study (Study 1), there was no significant difference observed between *Veramyst* and vehicle placebo spray for any secondary study endpoint for ocular efficacy (Table 16). In the 6-week study (Study

2), *Veramyst* 110 mcg QD was significantly ($P = 0.004$) more efficacious in reducing daily rTOSS versus vehicle placebo nasal spray (Table 16). Likewise, *Veramyst* provided statistically significant improvements compared with placebo in terms of the other secondary ocular assessments over 6 weeks (Table 16).

Table 16. Change from Baseline in Secondary Ocular Efficacy Endpoints from Studies in Adult and Adolescent Patients with Perennial Allergic Rhinitis

Study 1 (Weeks 1-4)* **Study 2 (Weeks 1-6)***	**Vehicle Placebo (n=153) (n=151)**	***Veramyst* 110 mcg QD (n=149) (n=151)**		
Endpoint	**LS Mean Change**	**LS Mean Change**	**LS Difference (95% CI)**	***P*- value**
Daily rTOSS				
Study 1	-1.24	-1.39	-0.15 (-0.52, 0.22)	0.428
Study 2	-1.41	-1.92	-0.506 (-0.85, -0.16)	0.004
AM pre-dose iTOSS				
Study 1	-1.14	-1.38	-0.238 (-0.63, 0.15)	0.228
Study 2	-1.26	-1.76	-0.491 (-0.85, -0.13)	0.007
AM rTOSS				
Study 1	-1.23	-1.42	-0.191 (-0.57, 0.18)	0.317
Study 2	-1.39	-1.92	-0.531 (-0.88, -0.19)	0.003
PM rTOSS				
Study 1	-1.25	-1.37	-0.120 (-0.50, 0.26)	0.532
Study 2	-1.44	-1.93	-0.496 (-0.84, -0.15)	0.005
KEY: LS=Least Square; CI=confidence Interval				
*entire treatment period				

Children Aged 2 to 11 Years

Unlike studies in adults and adolescents, the effect of *Veramyst* in treating ocular symptoms in children <12 years of age with PAR was not assessed in clinical trials.[23]

6. ADDITIONAL SAFETY INFORMATION

6.1 Studies Assessing Epistaxis

Background

Epistaxis has been associated with allergic rhinitis.[83,84] The greater susceptibility to epistaxis episodes in patients suffering from allergic rhinitis may be attributed to alterations in the nasal passages including pathophysiologic changes from chronic inflammation such as increased vascularization, and dryness and/or thinning of the nasal mucosa.[84,85,86] Epistaxis in patients with allergic rhinitis may also be attributed to direct nasal physical trauma secondary to allergic rhinitis symptoms (i.e., itchiness and/or sneezing) or improper administration of intranasal sprays.[84,86] Treatment associated episodes of epistaxis have also been reported, as adverse events, with the use of both corticosteroid and non-corticosteroid (i.e., azelastine, ipratropium) intranasal sprays.[86,87,55] Incidences as high as 17 to 23% have been reported for intranasal corticosteroids used in clinical trials, with longer treatment durations associated with increased event reporting.[86,88]

Short-Term Clinical Trial Experience

In 6 clinical trials of adults and adolescents 12 years and older, epistaxis occurred in 6% of patients treated with *Veramyst* 110 mcg once daily and 4% of vehicle placebo treated patients.[23] In 3 clinical trials of children, aged 2 to 11 years, epistaxis occurred in 5% and 4% of patients treated with *Veramyst* 55 and 110 mcg once daily and 4% of vehicle placebo treated patients.

Long-Term Clinical Trial Experience

Veramyst 110 mcg once daily (n=605) was compared with vehicle placebo (n=201) in a 52-week, long-term safety trial in adults and adolescents 12 years of age and older with perennial allergic rhinitis.[23,89,30] Adverse event data were collected via patient self-reported diary cards and interviews at each study visit. A detailed nasal examination of the turbinates, mucosa, septum, and secretions was also performed by the investigator at study visits 1 to 16/early withdrawal to evaluate nasal patency, mucosal edema, crusting and bleeding, and the presence and size of any polyps or ulcers. Any unfavorable changes from the Visit 1 assessment were recorded as an adverse event. Investigators made subjective assessments of intensity for each adverse event based on their clinical judgment using one of the following 3 categories: Mild - an event that was easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities; Moderate - an event that was sufficiently discomforting to interfere with normal everyday activities; Severe - an event that prevented normal everyday activities. Verbatim descriptions of each adverse event provided by the investigators were compiled using the Medical Dictionary for Regulatory Activities (MedDRA) “preferred terms" hierarchical listings. The preferred term “epistaxis” included a wide variety of verbatim descriptions provided by the investigators such as, appearance of bloody streaks in nasal mucus, blood in nasal mucus, blood tinged nasal mucus, bloody crusts in the nose, minor nasal bleeding, slight traces of blood, small blood spots in the nostril, as well as terms with descriptions of frank nasal bleeding such as epistaxis, nose bleed, nasal bleeding, blood clogged nostril, contact bleeding, and bloody nose.

Epistaxis occurred more frequently in patients receiving *Veramyst* (123/605, 20%) than in the placebo group (17/201, 8%). The episodes of epistaxis were of mild intensity in the majority of patients 17/17 in the placebo group and 83/123 in the group receiving *Veramyst*. The episodes were of moderate intensity in 39/123 patients and of severe intensity in 1/123 patients receiving *Veramyst*. Epistaxis led to the withdrawal of 15 patients (2%) in the group receiving *Veramyst* and no subjects in the placebo group. The majority of discontinuations due to epistaxis (10/15) occurred within the first 12 weeks of treatment and only one subject was withdrawn due to this adverse event after more than 6 months of treatment. Epistaxis reporting diminished as the study approached 52 weeks. There were no incidents of nasal septal perforation.

6.2 Studies Assessing Effect of Glaucoma/Cataracts

Background

The use of intranasal corticosteroids may result in the development of glaucoma and/or cataracts. As a result, patients with vision changes or a history of increased intraocular pressure (IOP), glaucoma and/or cataracts should be closely monitored. [23]

The development of glaucoma and cataract formation was assessed in a 52-week international study in 806 adult and adolescent patients ≥12 years of age with perennial allergic rhinitis (PAR) [89] and in a 12-week international study in 558 patients 2-11 years of age with PAR. [90] Patients in the 52-week study were randomized in a 3:1 ratio to treatment with either *Veramyst* 110mcg (n=605) or vehicle placebo (n=201) daily (QD). In the 12-week study, patients were randomized to receive *Veramyst* 55mcg (n=185), *Veramyst* 110mcg (n=185) or vehicle placebo (n=188) QD. Ophthalmic evaluations were performed by a licensed ophthalmologist or optometrist at baseline and Weeks 12, 24 and 52 for the 52-week study and at baseline and Week 12 for the 12-week study.

Ophthalmic evaluation of glaucoma included measurements of intraocular pressure (IOP) and funduscopic cup to disc percentage.[89] [90] Normal IOP typically ranges from 10-21 mmHg. However, measurements above this do not necessarily predict glaucoma. IOP is known to increase 1 mmHg every decade after 40 years of age in the western population. Typically, there is variance of 3-5 mmHg (10%) in standard readings on any given day. [91] In clinical trials with *Veramyst*, IOP assessment was measured via applanation tonometry with a sponsor-defined threshold limit of ≥21 mmHg. [89] [90]

Raised IOP is a risk factor for the future development of glaucoma[92,93,94] but it is not the only factor. [95] Abnormalities of the optic cup to disc ratio are also important; [94] [95] a funduscopic cup to disc percentage of 70% or higher has been associated with an increase in the relative risk of developing glaucoma. [96] In clinical trials with *Veramyst*, the sponsor-defined threshold limit for funduscopic cup to disc percentage was >66%. A new diagnosis of glaucoma during the study period was reported as an adverse event. [89,90]

Ophthalmic assessment of cataract formation included slit lamp examination of the cornea, iris and lens. Funduscopic examination of the retinal vasculature was also conducted. The presence or absence of cataracts was noted with each visit and if present, the type of cataract (cortical, nuclear or posterior subcapsular) was recorded. New cataracts detected during the study period were reported as an adverse event. (89,90)

There are primarily three types of age-related cataracts: nuclear, cortical and subcapsular. (97). Nuclear cataracts are the most common subtype and are most prevalent in European-derived populations. Nuclear cataracts develop very slowly, occur in the center of the lens, and are associated with the natural aging process. Cortical cataracts are the most common form in African- derived populations and can be associated with diabetes. Posterior subcapsular cataracts are the least prevalent subtype and often occur in combination with nuclear or cortical cataracts. Posterior subcapsular cataracts may be associated with diabetes, high myopia, retinitis pigmentosa, gyrate atrophy, radiation, and steroid therapy.

ASSESSMENTS FOR GLAUCOMA

Adult and Adolescent Patients

Intraocular Pressure (IOP)

The majority of patients (≥98%) had no change from baseline in IOP at any time in the study. (89) The occurrence of small mean changes from baseline in IOP seen in each eye were similar for both the *Veramyst* 110 mcg (n=605) and vehicle placebo (n=201) treatment groups (Table 17). Few patients (17 [2.8%] *Veramyst,* 4 [2%] vehicle placebo) had IOP measurements that were ≥21mmHg at any examination. Nine patients (5 [<1%] *Veramyst,* 4 [2%] vehicle placebo) had an IOP ≥21mmHg at baseline. The 5 patients randomized to treatment with *Veramyst* with high IOP at baseline had no further increase in IOP during the 52-week study period. Of these 5 patients, 1 patient had no further IOP measurements, 1 patient had an IOP of 22mmHg at a subsequent visit but values were lower than at baseline, and the remaining 3 patients had IOP measurements <21mmHg at all subsequent treatment assessments.

Table 17. Summary of Intraocular Pressure (IOP) (89)

	Vehicle Placebo (n=201)	***Veramyst* 110 mcg QD (n=605)**
Baseline IOP (n)	200	605
Left Eye: mean (mmHg)	14.3	14.2
Right Eye: mean (mmHg)	14.4	14.2
Change from Baseline		
Week 12 (n)	168	532
Left Eye: mean (mmHg)	-0.3	-0.2
Right Eye: mean (mmHg)	-0.3	-0.2
Week 24 (n)	156	501
Left Eye: mean (mmHg)	-0.3	-0.1
Right Eye: mean (mmHg)	-0.3	-0.1
Week 52 (n)	142	446
Left Eye: mean (mmHg)	0.1	0.1
Right Eye: mean (mmHg)	0.1	0.2

Twelve patients (2%), randomized to treatment with *Veramyst*, had IOP measurements of ≥21mmHg during the study period (Table 18). No patient had an IOP > 21mmHg at more than one treatment assessment. Eleven of twelve patients had IOP measurements of 21 mmHg (7 patients) and 22 mmHg (4 patients). Two patients with IOP measurements of 21mmHg at Week 12 had measurements < 21mmHg at subsequent visits at Weeks 24 and 52. One patient had an IOP measurement of 24mmHg in the left eye and 20 mmHg in the right eye at Week 52 (baseline 12 and 14mmHg, respectively). Upon follow-up examination 1 week post-treatment, IOP measurements of 22 mmHg were noted in both eyes.

Table 18. Change from Baseline in Intraocular Pressure (IOP) to ≥21mmHg in Adult and Adolescent Patients [89]

Evaluation	IOP	Vehicle Placebo	*Veramyst* 110 mcg QD
Week 12		(n=168)	(n=532)
	=21mmHg	1* (<1%)	2† (<1%)
	=22mmHg	0	0
	>22mmHg	0	0
Week 24		(n=156)	(n=501)
	=21mmHg	0	0
	=22mmHg	0	0
	>22mmHg	0	0
Week 52		(n=142)	(n=446)
	=21mmHg	0	5‡(1%)
	=22mmHg	0	4§ (<1%)
	>22mmHg	0	1‖¶ (<1%)

All patients were categorized as White/Caucasian.

*patient 19 years of age; †patients 18 and 52 years of age; ‡patients 16, 19, 40,46 and 49 years of age; §patients 16, 23, 49 and 53 years of age; ‖patient 33 years of age; ¶ Follow-up IOP reading at 1 week post-treatment noted as 22 mmHg in each eye.

Increased IOP was reported as an adverse event due to treatment for 4 patients (<1%) receiving *Veramyst* 110mcg. All were considered to be of mild intensity. Three patients had IOP measurements ≥21mmHg at Week 52 with lower measurements occurring previously during all other assessments. No glaucoma was detected in the study.

Funduscopic Cup to Disc Percentage

Changes from baseline in funduscopic cup measurements in each eye assessed by funduscopic cup to disc percentage were small and similar in both the *Veramyst* 110mcg and vehicle placebo treatment groups. Few patients (2 [<1%] *Veramyst*, 1 [<1%] vehicle placebo) had a funduscopic cup to disc percentage >66% at any examination. The majority of patients (>99%) had no change from baseline in funduscopic cup to disc percentage at any time in the study. No patient with a funduscopic cup to disc percentage >66% had an increase in IOP ≥21mmHg at any point in the study. Patients with an elevated IOP ≥21mmHg at Week 52 had a funduscopic cup to disc percentage of ≤20% at all assessments.

Pediatric Patients

Intraocular Pressure (IOP)

The majority of patients (≥ 98%) receiving *Veramyst* 55mcg (n=185), *Veramyst* 110mcg (n=185) or vehicle placebo (n=188) had no change from baseline in IOP. [90] The occurrence of small mean changes from baseline seen in each eye was similar between treatment groups. Few patients (≤1%) had an IOP ≥21mmHg at baseline or at Week 12. Eight patients had an IOP increase from baseline to endpoint to ≥ 21mmHg in at least one eye (Table 19). Five patients had an IOP increase ≥21mmHg in just one eye: two patients in each *Veramyst* group (1% each) compared with one patient (<1%) in the vehicle placebo group. Three patients had an IOP increase to ≥21mmHg in both eyes: two patients (1%) and 1 patient (<1%) in *Veramyst* 55mcg and 110mcg, respectively, compared with no patients in the vehicle placebo group.

Table 19. Change from Baseline in Intraocular Pressure (IOP) to ≥21mmHg in Pediatric Patients [90]

Evaluation	IOP	Vehicle Placebo	*Veramyst* 55mcg QD	*Veramyst* 110mcg QD
Week 12		(n=157)	(n=155)	(n=154)
	=21mmHg	1* (<1%)	2† (1%)	2‡ (1%)
	=22mmHg	0	0	1§ (<1%)
	>22mmHg	0	2‖ (1%)	0

All patients were categorized as White/Caucasian and/or mixed race/Hispanic/Latino or American Indian or Alaskan Native.

*patient 11 years of age; †patients 5 and 7 years of age; ‡patients both 8 years of age; §patient 4 years of age; ‖patients 10 and 11 years of age

Two reports of increased IOP ≥21mmHg (1 *Veramyst* 55mcg, 1 vehicle placebo) were considered drug-related adverse events. Additionally, two cases of increased IOP < 21 mmHg in the *Veramyst* treatment groups were reported as drug-related adverse events. All four cases of increased IOP were considered mild intensity with the exception of one moderate intensity case seen in the vehicle placebo group. No glaucoma, however, was detected in the study.

Funduscopic Cup to Disc Percentage

Small changes from baseline seen in each eye were similar across treatment groups. From baseline to Week 12, no patient in any treatment group had a shift to >66% in funduscopic cup to disc ratio measurements.

CATARACTS

Adult and Adolescent Patients

Slit Lamp and Funduscopic Examinations

Most funduscopic parameters assessed showed no abnormal changes over the 52-week treatment period in either the *Veramyst* 110mcg (n=605) or vehicle placebo (n=201) groups. [89] Cataracts were reported at baseline in 9 and 8 patients in the *Veramyst* 110mcg and vehicle placebo treatment groups, respectively. Four of 17 patients had posterior subcapsular cataracts. Sixteen of 17 patients were withdrawn prematurely from the study due to protocol violation.

Seven patients (6 [<1%] *Veramyst*, 1 [<1%] vehicle placebo) had cataracts identified in ophthalmic examinations that were not present at baseline (Table 20). Posterior subcapsular cataracts were reported as adverse events in 2 patients (<1%) receiving *Veramyst* 110mcg and 1 patient (<1%) receiving vehicle placebo. However, upon post-study evaluation in a patient in the *Veramyst* 110mcg group, the study ophthalmologist could no longer detect a posterior subcapsular cataract. [31] One report of bilateral cortical cataracts and one report of bilateral nuclear sclerotic cataracts were also reported as adverse events in patients receiving *Veramyst*.

Table 20. Number of New Cataracts Reported Over 52 Weeks in Adult and Adolescent Patients [89,31]

Type of Cataract	Vehicle Placebo (n=201)	*Veramyst* 110 mcg (n=605)
Posterior Subcapsular	1 (<1%)*	2 (<1%)†‡
Cortical	0	2 (<1%)§
Nuclear Sclerotic	0	3 (<1%)‖

All patients were categorized as White/Caucasian.
*patient 43 years of age; †patients 14 and 15 years of age; §patients 63 and 66 years of age; ‖patients 23, 66 and 72 years of age
‡includes 1 definite posterior subcapsular cataract and 1 trace posterior subcapsular cataract later determined undetectable by the study ophthalmologist upon post-study examination

Pediatric Patients

Slit Lamp and Funduscopic Examinations

Over the 12-week treatment period, most funduscopic parameters examined showed no abnormal changes across daily treatment with *Veramyst* 55mcg (n=185), *Veramyst* 110mcg (n=185) or vehicle placebo (n=188). [90] Four patients (2%) in the *Veramyst* 55mcg group reported a cataract in at least one eye compared with 2 patients (1%) in the vehicle placebo group (Table 21). No cataracts developed in patients receiving *Veramyst* 110mcg during the study although 2 patients had a posterior subcapsular cataract in at least one eye that was detected at both baseline and Week 12. Cataracts detected at Week 12 in the two patients (1%) receiving vehicle placebo and one (<1%) receiving *Veramyst* 55mcg were reported as adverse events.

Table 21. Number of New Cataracts Reported Over 12 Weeks in Pediatric Patients [90]

Type of Cataract	Vehicle Placebo (n=188)	*Veramyst* 55mcg (n=185)	*Veramyst* 110mcg (n=185)
Posterior Subcapsular	3*‡(1%)	5†‡ (2%)	0
Cortical	0	0	0
Nuclear Sclerotic	0	0	0
Ethnicity of patients varied and included White/Caucasian, African American, American Indian, Hispanic and mixed race. *patients 7 and 11 years of age; †patients 5, 6, 11 and 11 years of age ‡One patient in each group had a new cataract reported in both eyes			

6.3 Studies Assessing Effect of HPA Axis in Adults and Adolescents

Background

Two tests commonly used to evaluate hypothalamic-pituitary-adrenal (HPA) axis function are the morning (AM) plasma cortisol and synthetic adrenocorticotropic hormone (ACTH) (cosyntropin) stimulation test. The advantages of both tests are the simplicity and safety of each. However, plasma cortisol fluctuates throughout a 24-hour period; therefore, it is necessary to standardize the time of day at which the AM plasma cortisol is drawn, preferably 8 am. Even with time standardization, there is a wide range of cortisol levels. Additionally, venipuncture is stressful to many people and this stress itself may elevate resting levels. Thus, individual cortisol levels are not ideal indicators of HPA function. Cosyntropin stimulation reveals the resting state and the reserve capacity of the adrenal cortex. A normal response (rise in cortisol) suggests that HPA function is normal; however, only the adrenocortical component of the system is being tested.[98] Measurements of plasma cortisol concentration performed every 2 hours during a 6 or 8 hour infusion of cosyntropin stimulation constitute the most reliable means of determining normality of the adrenal cortex. [99]

In additional to plasma cortisol testing, urinary free cortisol (UFC) also provides an excellent measure of adrenocortical function, but its accuracy is easily diminished due to patient compliance problems with urine collection procedures. Creatinine content may be measured in an attempt to assess completeness of urine collection. Twenty-four hour UFC may not differentiate low-normal and abnormal results. Similar problems can be seen with overnight urinary cortisol measurements, and the test has not been standardized with established normal values. Thus, UFC, overnight cortisol measurements, and individual cortisol levels are not ideal indicators of HPA function.[98,100]

Another factor to consider when evaluating HPA axis function is the time of administration of the exogenous corticosteroid. Steroid administration at a time when plasma cortisol levels are low (late in the evening) will suppress ACTH production more than if given in the early morning when endogenous cortisol levels are at their peak.[101]

Clinical Trial Experience in Adults and Adolescents

6-week Domiciled Setting

A 6-week, randomized, double blind, parallel group study was specifically designed to assess whether cortisol production, as a measure of Hypothalamic-Pituitary-Adrenal (HPA) axis function, was suppressed by treatment with *Veramyst* in patients 12 to 65 years of age with perennial allergic rhinitis (PAR).[23,102] Patients were assigned in a 4:4:1 ratio to one of the following treatment groups: *Veramyst* 110 mcg once daily (QD) plus placebo capsules for the last 7 days, vehicle placebo aqueous nasal spray QD plus placebo capsules for the last 7 days, or vehicle placebo aqueous nasal spray QD plus encapsulated prednisone 10 mg QD for the last 7 days. Prednisone was administered for the final 7 days of the treatment period as a positive control group to confirm assay sensitivity. Patients were domiciled in a clinic setting at the beginning and end of 6 weeks of treatment to standardize, control and monitor the collection of blood and urine samples over 24 hours to assess adrenal function. The change from baseline (expressed as a ratio) in 24-hour serum cortisol weighted mean was the primary study endpoint. A secondary endpoint was the change from baseline in 24-hour urinary free cortisol excretion. Analyses of serum and urinary cortisol data demonstrated comparability between *Veramyst* 110 mcg QD and placebo in terms of HPA axis suppression. Of note there was wide variability in the analyses of treatment differences between *Veramyst* and placebo

in 24-hour urinary cortisol excretion. Prednisone showed significant reduction from baseline in serum cortisol assessments which confirmed the sensitivity of the model. Table 22 summarizes these results.

52-week Non-domiciled Setting

In a 52-week, long-term safety trial in adults and adolescents 12 years of age and older with PAR, once daily (QD) administration of *Veramyst* 110 mcg (n = 605) was compared with placebo nasal spray (n = 201).[23,103] Adrenal function was assessed by 24-hour urinary cortisol excretion in a non-domiciled setting in a subset of patients who received *Veramyst* (n = 370) or placebo (n = 120). Intent-to-treat patients whose urine samples were considered to have confounding factors that would have affected the interpretation of results were excluded from the analysis. Urinary cortisol excretion was assessed prior to randomization and again at weeks 12, 24 and 52. After 52 weeks, the mean change from baseline in 24-hour urinary cortisol excretion was not statistically different between the group treated with *Veramyst* and the placebo group. Of note was the wide variability in the confidence intervals for the treatment difference between *Veramyst* and placebo (Table 22).

Table 22. Effect of *Veramyst* on Hypothalamic-Pituitary-Adrenal (HPA) Axis Function in Patients 12 to 65 Years of Age

Analytical Method	Least Square Mean			Treatment Difference (95% CI)	Treatment Ratio (95% CI)
	Placebo (n)	Fluticasone Furoate 110mcg QD (n)	Prednisone* 10mg QD (n)		
6-week Domiciled Study [23,102]					
24-hour serum cortisol weighted mean (nmol/L)	0.99 (n=44)	0.97 (n=43)	—	—	0.98 (0.89†, 1.07)
24-hour serum cortisol weighted mean (nmol/L)	0.99 (n=44)	—	0.49 (n=12)	—	0.49 (0.43, 0.57)
24-hour serum cortisol (mcg/dL)	0.08 (n=44)	-0.38 (n=43)	—	-0.47 (-1.31, 0.37)	—
24-hour serum cortisol (mcg/dL)	0.08 (n=44)	—	-4.49 (n=12)	-4.57 (-5.83, -3.31)	—
24-hour urinary cortisol (mcg/day)	-3.48 (n=42)	-1.16 (n=43)	—	2.32 (-6.76, 11.39)	—
52-week Non-domiciled Study [23]					
24-hour urinary cortisol (mcg/day)	3.34 (n=120)	5.84 (n=370)	—	2.50 (-5.49, 10.49)	—

*Domiciled Study only - prednisone administered for the final 7 days of the treatment period as a positive control to confirm assay sensitivity. Urinary cortisol data were not available for the prednisone group due to the inability of the assay used by the lab to read cortisol excretion. †Non-inferiority was demonstrated as the lower limit of the 2-sided confidence interval (CI) for the geometric mean ratio of fluticasone furoate and placebo was greater than the predefined unit of 0.80.

6.4 Studies Assessing Effect of HPA Axis in Children

Clinical Trial Experience in Children Less Than 12 Years of Age

6-week Domiciled Setting

A 6-week, randomized, double blind, parallel group study was specifically designed to assess whether cortisol production, as a measure of Hypothalamic-Pituitary-Adrenal (HPA) axis function, was suppressed by treatment with *Veramyst* in children 2 to 11 years of age with perennial allergic rhinitis (PAR). [23,104] Patients were treated once daily with *Veramyst* 110 mcg or placebo nasal spray. No active control arm was included in this study as it was considered inappropriate to administer an HPA axis suppressive agent to otherwise healthy children. Therefore treatment compliance was important to ensure robust data for evaluation. Several different means of assessing compliance were utilized including diary cards and use of videophone equipment to observe patients taking their daily study medication. The primary study endpoint was the change from baseline (expressed as a ratio) in 24-hour serum cortisol weighted mean. The change from baseline in 24-hour urinary free cortisol excretion was also evaluated. Patients were domiciled in clinic for collection of 24-hour urinary cortisol. Analyses of serum and urinary cortisol data demonstrated

comparability between *Veramyst* 110 mcg QD and placebo in terms of HPA axis suppression. Of note there was a wide variability in the analyses of treatment differences between *Veramyst* and placebo for 24-hour urinary cortisol excretion. Table 23 summarizes these results.

12-week Non-domiciled Setting

In a 12-week safety and efficacy trial in children 2 to 11 years of age with PAR, once daily administration of *Veramyst* 55 mcg (n = 185) or *Veramyst* 110 mcg (n = 185) was compared with placebo nasal spray (n = 188).[23,105] In a non-domiciled setting, adrenal function was assessed by measurement of 24-hour urinary free cortisol in a subset of patients who were 6 to 11 years of age (103 to 109 patients per group) before and after 12 weeks of treatment. No patient in any treatment group had 24-hour urinary cortisol excretion below the normal range at baseline or at endpoint. After 12 weeks of treatment, there was a decrease in mean 24-hour urinary cortisol excretion from baseline in both groups treated with *Veramyst* compared with placebo. Neither active treatment was statistically different from placebo. Of note there was wide variability in the analyses of treatment differences between *Veramyst* and placebo for 24-hour urinary cortisol excretion (Table 23).

Table 23. Effect of *Veramyst* on Hypothalamic-Pituitary-Adrenal (HPA) Axis Function in Children Less Than 12 Years of Age

Analytical Method	Least Square Mean			Treatment Difference (95% CI)	Treatment Ratio (95% CI)
	Placebo (n)	Fluticasone Furoate 55mcg QD (n)	Fluticasone Furoate 110mcg QD (n)		
6-week Domiciled Study in Children 2 to 11 Years of Age[23,104]					
24-hour serum cortisol (nmol/L)	0.97 (n=49)	—	0.94 (n=52)	—	0.97 (0.88*, 1.07)
24-hour serum cortisol (mcg/dL)	-0.23 (n=47)	—	-0.34 (n=48)	-0.11 (-0.88, 0.66)	—
24-hour urinary cortisol (mcg/day)	1.92 (n=41)	—	0.49 (n=43)	-1.43 (-5.21, 2.35)	—
12-week Non domiciled Study in Children 6 to 11 Years of Age[23]					
24-hour urinary cortisol (mcg/day)	0.08 (n=107)	-2.93 (n=109)	—	-3.01 (-6.16, 0.13)	—
24-hour urinary cortisol (mcg/day)	0.08 (n=107)	—	-2.07 (n=103)	-2.14 (-5.33, 1.04)	—
*Non-inferiority was demonstrated as the lower limit of the 2-sided confidence interval (CI) for the geometric mean ratio of fluticasone furoate and placebo was greater than the predefined unit of 0.80.					

6.5 Studies Assessing Effect on Growth in Children

Background

Controlled clinical studies have shown that intranasal corticosteroids may cause a reduction in growth velocity in pediatric patients.[23] This effect has been observed in the absence of laboratory evidence of Hypothalamic-Pituitary-Adrenal (HPA) axis suppression, suggesting that growth velocity is a more sensitive indicator of systemic corticosteroid exposure in pediatric patients than some commonly used tests of HPA axis function. The long term effects of reduction in growth velocity associated with intranasal corticosteroids, including the impact on final adult height, are unknown. The potential for "catch up" growth following discontinuation of treatment with intranasal corticosteroids has not been adequately studied. The growth of pediatric patients receiving intranasal corticosteroids should be monitored routinely (e.g., via stadiometry). The potential growth effects of prolonged treatment should be weighed against the clinical benefits obtained and the risks/benefits of treatment alternatives. To minimize the systemic effects of intranasal corticosteroids each patient's dose should be titrated to the lowest dosage that effectively controls his/her symptoms.

Short-Term Lower Leg Growth

A controlled cross-over study was conducted in 58 prepubertal children with allergic rhinitis aged 6 to 11 years to evaluate the effect of *Veramyst* 110 mcg once daily (QD) for 2 weeks on short-term lower-leg growth as measured by knemometry.[106] Patients were randomized to a double-blind treatment sequence of either *Veramyst* 110 mcg QD followed by vehicle placebo QD for 2 weeks, or vehicle placebo QD followed by *Veramyst* 110 mcg QD for 2 weeks. Each treatment sequence was separated by a 2-week washout period.

The primary safety endpoint was the mean growth rate (mm/wk) in lower-leg length over 2 weeks. The primary analysis was conducted on the Growth Population (N=53) which excluded patients without reliable lower-leg growth data, or who received protocol-prohibited medications. In this study, *Veramyst* was considered to be non-inferior to placebo if the lower limit of the two-sided 95% confidence interval (CI) for the treatment difference (*Veramyst* minus placebo) was greater than or equal to -0.20 mm/wk (approximately 40-50% of the expected placebo growth rate). The lower limit of the 95% CI for the treatment difference was -0.13mm/wk, which was greater than the non-inferiority margin of -0.20mm/wk (Table 24). These results showed that *Veramyst* was non-inferior to placebo with respect to lower-leg growth rate.

Table 24. Lower-Leg Growth Rate (mm/wk)

	Vehicle Placebo	***Veramyst* 110 mcg QD**
	(N= 53)	**(N= 53)**
Comparison against Placebo		
LS Mean (SE)	0.42 (0.04)	0.40 (0.04)
LS Mean Difference	-0.016	
P-value against Placebo*	0.78	
95% C.I.	-0.13, 0.10	
*ANCOVA adjusted for baseline lower-leg growth rate, age, and gender.		
LS=least square		
SE=standard error		
LS Mean Difference=LS mean change in active - LS mean change in placebo		
CI=confidence interval		

The above study was a 2-week short-term assessment. There are no longer term studies. The potential for *Veramyst* to cause growth suppression in susceptible patients or when given at higher than recommended dosages cannot be ruled out.

7. COMPARATIVE DATA

7.1 Clinical Comparison with Fluticasone Propionate Nasal Spray

Comparative Study

A Japanese, multicenter, randomized, placebo-controlled, double-blind study was conducted to demonstrate the non-inferiority of *Veramyst* compared with FPNS.[107] Patients enrolled in the study were aged 16 years or older with a history of SAR (cedar pollinosis) diagnosed at least 2 years before, who had positive allergy tests and an average of ≥ 4 on the 3 TNSS (sneezing, rhinorrhea, and nasal congestion) in the consecutive 4 days prior to the screening period. Patients (N=446) received two weeks of treatment with either once-daily *Veramyst* 110 mcg, once-daily fluticasone furoate nasal spray (FFNS) placebo, twice-daily FPNS 200 mcg/day or twice-daily FPNS placebo.

Efficacy Results

The primary efficacy endpoint for this study was mean change from baseline over the entire treatment period (14 days) in the 3 TNSS, defined as the sum (0 to 9) of three individual symptom scores for sneezing, rhinorrhea and nasal congestion where each symptom was scored on a scale of 0 to 3 in the nasal allergy diary.

The primary efficacy endpoint mean change from baseline over the entire treatment period in the 3TNSS had a 95% confidence interval (CI) of -0.51, 0.17 for the adjusted mean difference between *Veramyst*

110 mcg and FP groups. Since the upper limit of the CI was lower than the non-inferiority margin of 0.75, the non-inferiority of *Veramyst* 110 mcg to FPNS was proven (Table 25). Compared with FFNS placebo, patients receiving *Veramyst* had significant improvement from baseline in 3TNSS over the entire treatment period.

Table 25. Mean Change from Baseline over Entire the Entire Treatment Period in TNSS (per-protocol analysis)

	FPNS 100 mcg BID (200 mcg/day) (n = 144)	***Veramyst* 110 mcg QD (110 mcg/day) (n = 147)**
Mean ± SD	-1.3 ± 1.70	-1.4 ± 1.70
Adjusted mean (SE)	-1.06 (0.142)	-1.23 (0.140)
Adjusted mean difference from FPNS (95% CI)	-0.173 (-0.51, 0.17)	
BID = twice daily, QD = once daily		

Secondary endpoints included mean changes from baseline over Week 1 and Week 2 in 3TNSS, mean percent change from baseline over the entire treatment period in 3TNSS, mean change from baseline over the entire treatment period in 4 Total Nasal Symptom Score (4TNSS, included nasal itching), mean changes from baseline over Week 1 and Week 2 in 4TNSS, mean percent change from baseline over the entire treatment period in 4TNSS, mean changes from baseline over the entire treatment period in individual nasal symptom (sneezing, rhinorrhea, nasal congestion, nasal itching) scores, mean changes from baseline over Week 1 and Week 2 in individual nasal symptom scores, change from baseline at Week 1 and Week 2 or Early Withdrawal in the score of individual nasal findings (swelling of inferior turbinate mucosa, color of inferior turbinate mucosa, watery secretion volume and nature of rhinorrhea, under rhinoscopy).

No secondary endpoints were evaluated for statistical significance between the *Veramyst* 110 mcg and FPNS study groups. The *Veramyst* 110 mcg group demonstrated statistically significant improvements in all secondary endpoints compared with the corresponding placebo group.

Safety Results

The safety endpoints measured included adverse events (AEs), clinical laboratory test values (hematology, clinical chemistry), and adrenocortical function test (serum cortisol levels). Adverse events reported in the *Veramyst* 110 mcg group were similar in nature and incidence to those reported in the *Veramyst* placebo group. There were no adverse events specific to the *Veramyst* 110 mcg group (Table 26). At Week 2/Early Withdrawal, there was no significant difference in the mean change from baseline in serum cortisol in any treatment group.

Table 26. Adverse Events* That Occurred ≥ 1% in the Active Treatment Groups

	FP NS Placebo (n = 74)	**FPNS 100 mcg BID (200 mcg/day) (n = 148)**	**FFNS Placebo (n = 72)**	***Veramyst* 110 mcg QD (110 mcg/day) (n = 149)**
WBC increased	0	1 (< 1%)	0	2 (1%)
Epistaxis	3 (4%)	2 (1%)	0	0
*Casual relationship to study treatment cannot be ruled out. BID = twice daily, QD = once daily				

7.2 Clinical Comparison with Fexofenadine

Comparative Studies

Two randomized, double-blind, double-dummy, placebo-controlled, parallel-group, 2-week clinical trials evaluated the comparative efficacy and safety of intranasal *Veramyst* and oral fexofenadine in patients ≥12 years with ≥2 year history/diagnosis of seasonal allergic rhinitis (SAR) to mountain cedar (Study 1) or ragweed (Study 2) (positive skin tests).[24,108,25] Prior to randomization, patients were required to have met

the following minimum symptom criteria with average scores on any 4 of the last 7 assessments during the 5-21 day pre-treatment screening period: nighttime symptoms score (NSS) ≥4.5, congestion score on awakening assessed for NSS ≥2, daytime reflective total nasal symptoms scores (D-rTNSS) ≥6, reflective nasal congestion score ≥2, daytime reflective total ocular symptoms score (D-rTOSS) ≥4, and diary completion >80%. Randomized patients received either intranasal *Veramyst* 110 mcg and an oral placebo capsule (Study 1: n=312, Study 2: n=224), oral fexofenadine 180 mg and intranasal vehicle-placebo nasal spray (Study 1: n=311, Study 2: n=227), or intranasal vehicle-placebo nasal spray and oral placebo once daily (Study 1: n=313, Study 2: n=229).

The primary efficacy endpoint was the mean change from baseline (MCFB) over the 2-week treatment period in the nighttime symptoms score (NSS) which assessed the impact of nighttime nasal symptoms on sleep using a validated questionnaire. The NSS is obtained from the subject's ratings on awakening each morning, prior to taking their treatment medications, of 3 questions relating to nasal congestion on awakening, nighttime awakenings due to nasal symptoms, and the degree of difficulty going to sleep due to nasal symptoms. Each question is rated utilizing a 0 (none) to 3 (severe) scale.

Secondary efficacy endpoints included MCFB over the 2-week treatment period in reflective total nasal symptoms scores (rTNSS), comprised of nasal itching, sneezing, nasal congestion, and rhinorrhea, and reflective total ocular symptom scores (rTOSS), comprised of eye itching/burning, tearing/watering, and redness, obtained from 12-hour assessments. Terms used for the 12-hour assessment periods represented the period being assessed. Assessments performed in the morning were termed nighttime (N), and assessments performed in the evening were termed daytime (D). The daytime and nighttime assessments were averaged to derive "24-hour" values which were previously termed "daily" in other fluticasone furoate studies. The names of these assessments were changed in this study to coincide with the primary endpoint, the nighttime symptoms score, which was evaluted in the morning upon awakening. Nasal and ocular symptoms were also rated instantaneously (i) each morning prior to dosing to assess duration of action.

Peak inspiratory nasal flow (PNIF), a measurement of nasal congestion using a hand-held inspiratory flow meter, was also assessed by twice daily patient measurements (in the morning (AM) prior to taking study medication and in the evening (PM)).

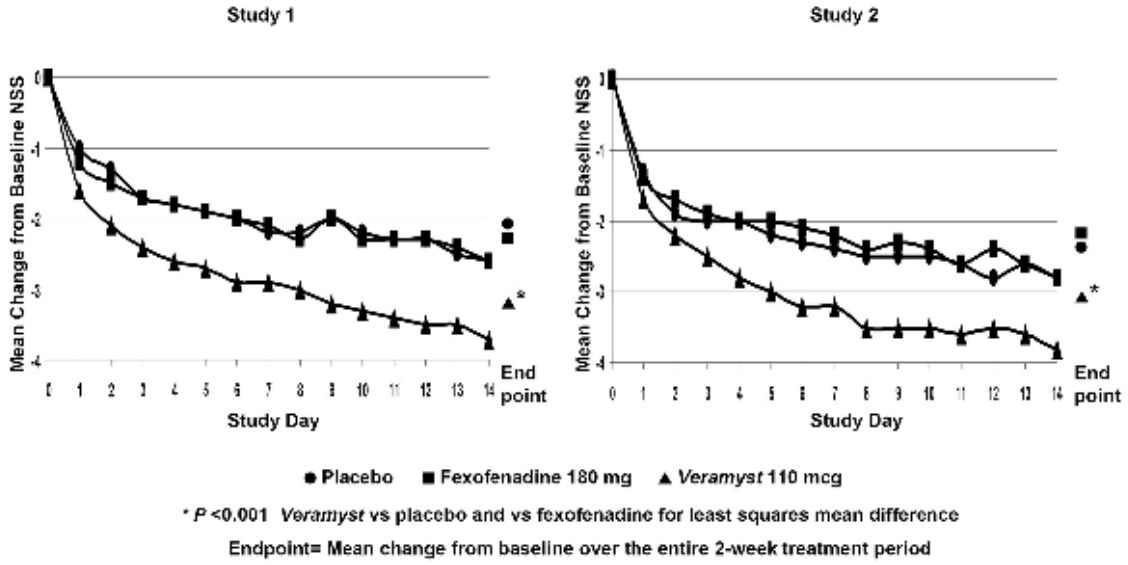
Sleep related quality of life (QOL) was also evaluated by MCFB in the nocturnal rhinoconjunctivitis quality of life questionnaire (NRQLQ) global score. The NRQLQ is a 16-item, self-administered, disease-specific (allergic rhinitis), QOL instrument used to measure the functional problems that are most troublesome to patients with nocturnal allergy symptoms over a 1-week period by assessing four individual NRQLQ domains (sleep problems, sleep time problems, symptoms on waking in morning, practical problems) and an overall global score.

Safety was assessed by adverse events, vital signs, physical examination, and nasal examination.

Efficacy Results

In both studies, *Veramyst* provided significant improvements in the NSS compared to both fexofenadine and placebo (P <0.001), as illustrated in Figure 17. No difference in the control of nighttime symptoms was seen between fexofenadine and placebo.

Figure 17. Mean Change from Baseline in Nighttime Symptoms Scores (NSS)



In both studies, *Veramyst* also produced significantly greater improvements in all secondary nasal efficacy endpoints (daytime, nighttime, 24-hr, pre-dose TNSS) than fexofenadine or placebo (P <0.001). In Study 2, *Veramyst* provided significantly greater improvements in ocular symptoms (daytime, nighttime, 24-hour, and instantaneous total ocular symptoms scores) compared with fexofenadine and placebo (P ≤0.034). In Study 1, improvements in ocular symptoms with *Veramyst* were significantly greater compared with placebo P ≤0.007) and were comparable with the improvements seen with fexofenadine (P ≥0.058). (Table 27). The PNIF (AM and PM) and NRQLQ (global score) were also significantly improved by *Veramyst* compared with fexofenadine and placebo (P <0.001) in both studies.

Table 27. - See Appendix

Safety

Adverse events reported with *Veramyst* were similar in nature and incidence to those reported in the fexofenadine and placebo groups (Table 28).

Table 28. Adverse Events Occurring ≥1% and More Common than Placebo

Adverse Event	Placebo (Study 1: n=313) (Study 2: n=229)	Fexofenadine (Study 1: n=311) (Study 2: n=227)	*Veramyst* (Study 1: n=312) (Study 2: n=224)
Headache (n,%)	11 (4) 6 (3)	10 (3) 9 (4)	12 (4) 10 (4)
Epistaxis (n,%)	5 (2) 2 (<1)	1 (<1) 4 (2)	7 (2) 0
Pharyngolaryngeal Pain (n,%)	4 (1) 1 (<1)	1 (<1) 3 (1)	5 (2) 3 (1)
Pyrexia (n,%)	2 (<1) 0	4 (1) 0	1 (<1) 0

8. OTHER STUDIED USES

8.1 Use in Patients with Vasomotor Rhinitis (VMR)

Background

Vasomotor rhinitis (VMR) is typically defined as a chronic noninfectious rhinitis characterized by nasal symptoms for which an immunoglobulin E (IgE)-mediated mechanism cannot be demonstrated.[109] [43] It is characterized by perennial nasal symptoms that primarily include nasal congestion, rhinorrhea and postnasal drip. The symptoms are usually the same as in allergic rhinitis, but eye symptoms are less frequent and nasal blockage more prominent.[109] VMR is considered to be a subclass of perennial non-allergic rhinitis (PNAR), which accounts for approximately 50% of rhinitis sufferers. [43] VMR is commonly encountered in clinical practice, with an estimated prevalence between 5% and 10% in the general population and a higher prevalence in females than males.[110]

Based on literature, the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines, and leading medical experts, VMR has been described to include patients who experience worsening of their rhinitis symptoms by both weather/temperature change and inhaled/strong odor irritant (i.e., smoke, perfume, paint, other strong odors) triggers.[109] [43,111,112,113] There is however no scientific data that proves specific triggers, such as weather/temperature changes or respiratory irritants generate rhinitis symptoms by the same biologic pathway. It has been postulated that the biological events that result in rhinitis symptoms from weather related changes are likely to be different than those events leading to symptoms after exposure to respiratory irritants.[114] Thus, studying the effects of potential new treatments would necessitate study inclusion/exclusion criteria based on patients' predominant symptom trigger categories. Studying patients with rhinitis symptoms predominantly triggered by weather/temperature changes would necessitate the exclusion of patients whose predominant or only triggers of rhinitis symptoms were respiratory irritants, such as smoke, perfume, paint, and other strong odors. This new inclusion/exclusion study criteria based on predominant triggers is distinctly different than that of previously published PNAR clinical trials that have documented beneficial treatment effects in PNAR patients. [115,116]

Clinical Trials

The efficacy and safety of *Veramyst* in treating patients with VMR whose symptoms were triggered predominantly by weather/temperature changes was evaluated in 2 identically designed multi-centered, randomized, double-blind, placebo-controlled, parallel-group 4-week clinical trials.[114,117] For these studies, VMR was defined as patients with a two year clinical history of VMR, negative prick skin tests to seasonal and perennial allergens and a positive prick skin test to histamine, normal sinus radiograph (Waters view), negative nasal cytology for eosinophils, and confirmation that a weather/temperature change trigger was the predominant trigger group that made their rhinitis symptoms worse. Following a screening period, patients 12 years and older with VMR meeting specified symptom criteria were randomized to 4 weeks' treatment with either *Veramyst* 110 mcg once daily (n=174 and n=178, studies 1 and 2, respectively) or vehicle placebo nasal spray (n=173 and n=172, studies 1 and 2, respectively). All efficacy measures were based on patient self-assessments. The primary efficacy measure was the mean change from baseline over the entire treatment period in daily reflective, total nasal symptom scores (rTNSS). Key secondary measures were the mean change from baseline over the entire treatment period in morning (AM) pre-dose instantaneous total nasal symptom scores (iTNSS) and an overall evaluation of response to therapy. Other secondary efficacy measures included mean change from baseline over the entire treatment period in AM rTNSS and PM rTNSS, individual daily reflective nasal symptom scores and AM pre-dose instantaneous nasal symptom scores for rhinorhea, nasal congestion and postnasal drip, individual AM reflective, and PM reflective, nasal symptom scores for rhinorrhea, nasal congestion and postnasal drip, and mean percent change from baseline over the entire treatment period in daily rTNSS and AM pre-dose iTNSS, and time to onset/time to maximum effects.

In the first study, *Veramyst* 110 mcg once daily did not demonstrate a statistically significant difference compared with placebo for the primary endpoint, the mean change from baseline over the entire treatment period in daily rTNSS (LS mean difference = 0.094; P=0.604).[114] Similar findings were observed for the key secondary endpoint, mean change from baseline in AM pre-dose iTNSS (LS mean difference = 0.061; P=0.729). For the other key secondary endpoint, overall evaluation of response to therapy, 40% of patients receiving *Veramyst* reported significant and moderate improvement compared with 34% of those

patients receiving placebo. The treatment difference for overall response to therapy was not significant (*P*=0.064). No significant differences between treatment groups were observed for any of the other secondary endpoints.

In the second study, *Veramyst* 110 mcg once daily did not demonstrate a statistically significant difference compared with placebo for the primary endpoint, the mean change from baseline over the entire treatment period in daily rTNSS (LS mean difference = -0.335; *P*=0.0504).[117] For the key secondary endpoint, mean change from baseline in AM pre-dose iTNSS, a statistically significant difference in the treatment groups over the entire treatment period was observed in favor of *Veramyst* (LS mean difference = -0.393; *P*=0.027). For the other key secondary endpoint, overall evaluation of response to therapy, 41% of patients receiving *Veramyst* reported significant or moderate improvement compared with 37% of those patients receiving placebo. The treatment difference for overall response to therapy was not significant (*P*=0.184). Statistical significance was demonstrated in favor of *Veramyst* for some other secondary endpoints (mean percent change from baseline in AM pre-dose iTNSS, mean change from baseline in AM pre-dose instantaneous symptom score for nasal congestion, and mean change from baseline in AM reflective symptom score for rhinorrhea), however, no consistent pattern was observed.

9. EVIDENCE TABLES

9.1 Clinical Summary Table for Seasonal Allergic Rhinitis in Adults and Adolescents

Table 29. - See Appendix

9.2 Clinical Summary Table for Perennial Allergic Rhinitis in Adults and Adolescents

Table 30. - See Appendix

9.3 Clinical Summary Table for Seasonal Allergic Rhinitis in Children

Table 31. - See Appendix

9.4 Clinical Summary Table for Perennial Allergic Rhinitis in Children

Table 32. - See Appendix

9.5 Clinical Summary Table on Occurence of Hypothalamic-Pituitary-Adrenal (HPA) Axis Effects

Table 33. - See Appendix

9.6 Clinical Summary Table of Long-Term Safety

Table 34. - See Appendix

9.7 Clinical Summary Table Comparison with Fluticasone Propionate Nasal Spray

Table 35. - See Appendix

9.8 Clinical Summary Table Comparison with Fexofenadine

Table 36. - See Appendix

10. OUTCOME EVALUATIONS

10.1 Effect of *Veramyst* on Quality of Life

Background

The Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) is a 28-item, self-administered, disease specific instrument used to gather information about how allergic rhinitis patients perceive the impact of the disease on their quality of life. [119] The RQLQ assesses the impact of allergic rhinitis treatment on 7 domains: activity limitations (3 items), sleep problems (3 items), non-nose/eye symptoms (7 items), practical problems (3 items), nasal symptoms (4 items), eye symptoms (4 items) and emotional function (4 items). Perceptions of impact are rated on a 7-point scale where 0 = no impairment and 6 = maximum impairment. An overall quality of life score is calculated from the mean score of all items.

Quality of Life Assessments in Patients Aged 12 and Older with Seasonal Allergic Rhinitis (SAR)

The effect of *Veramyst* 110 mcg once daily (QD) on quality of life was evaluated in 3, 2-week, double-blind, randomized, parallel-group, placebo controlled trials.[73,75,76] Studies 1 (N = 299), 2 (N = 285), and 3 (N = 302) consisted of patients ≥ 12 years of age who had a diagnosis of SAR due to ragweed, grass pollen, and mountain cedar, respectively. Patients in all 3 studies were required to reside within a geographical region where exposure to the particular allergen was expected to be significant during the entire study period.

Following a 5- to 21-day screening period, patients meeting specified symptom criteria were randomized to 2 weeks of treatment with intranasal *Veramyst* 110 mcg or vehicle placebo QD in the morning. Patients completed the RQLQ at baseline prior to study drug administration and at the end of the study.

At the endpoint of Study 1, the mean difference was statistically significant for the patients treated with *Veramyst* compared with placebo for the overall RQLQ score as well as the individual domains except for eye symptoms (Table 37).[73] A clinically meaningful improvement (absolute difference of ≥0.5 in the mean change from baseline over placebo) was also seen by patients treated with *Veramyst* for the overall RQLQ score and for all but the domain of eye symptoms.

In Study 2, patients treated with *Veramyst* experienced a statistically significant improvement over placebo in overall RQLQ scores and in each of the 7 individual domains (Table 37). [75] The clinically meaningful improvement was achieved overall, and in the individual domains, except for non-hay fever symptoms and eye symptoms.

In Study 3 patients treated with *Veramyst* experienced statistically significant and a clinically meaningful improvement in overall RQLQ scores, and in each of the 7 individual domains compared with placebo (Table 37). [76]

Table 37. Change from Baseline in RQLQ Scores in Adult and Adolescent Patients with SAR

Weeks 1-2*	**Vehicle Placebo**	***Veramyst* 110 mcg QD**		
Study Number				
Study 1	(n = 148)	(n = 151)		
Study 2	(n = 144)	(n = 141)		
Study 3	(n = 150)	(n = 152)		
Endpoint (Scale 0-6)†	**LS Mean Change**	**LS Mean Change**	**LS Mean Difference (95% CI)**	***P* Value**
RQLQ Overall				
Study 1	-1.16	-1.77	-0.60 (0.93, -0.28)‡	<0.001
Study 2	-1.53	-2.23	-0.70 (-0.99, -0.41)‡	<0.001
Study 3	-0.97	-1.66	-0.69 (-1.08, -0.30)‡	<0.001
Activities				
Study 1	-1.25	-1.96	-0.72 (-1.09, -0.35)‡	<0.001
Study 2	-1.79	-2.68	-0.89 (-1.35, -0.44)‡	<0.001
Study 3	-1.01	-1.73	-0.72 (-1.19, -0.25)‡	0.003
Sleep				
Study 1	-1.08	-1.81	-0.72 (-1.11, -0.34)‡	<0.001
Study 2	-1.44	-2.04	-0.60 (-0.92, -0.28)‡	<0.001
Study 3	-1.00	-1.50	-0.51 (-0.95, -0.07)‡	0.023
Non-Nose/Eye Symptoms (non-hay fever)				
Study 1	-1.1	-1.63	-0.54 (-0.89, -0.19)‡	0.003
Study 2	-1.46	-1.77	-0.31 (-0.60, -0.02)	0.036
Study 3	-0.92	-1.49	-0.57 (-0.98, -0.17)‡	0.006
Practical Problems				
Study 1	-1.22	-1.99	-0.77 (-1.16, -0.39)‡	<0.001
Study 2	-2.00	-2.74	-0.74 (-1.11, -0.37)‡	<0.001

*entire treatment period
†perceptions of impact of treatment rated on a 7-point scale (0=no impairment and 6=maximum impairment)
‡clinically meaningful improvement = absolute difference of ≥0.5 in the mean change from baseline over placebo
CI = Confidence Interval; LS = Least Square

Weeks 1-2*	**Vehicle Placebo**	***Veramyst* 110 mcg QD**		
Study 3	-1.05	-1.97	-0.92 (-1.36, -0.48)‡	<0.001
Nasal Symptoms				
Study 1	-1.16	-2.03	-0.87 (-1.25, -0.49)‡	<0.001
Study 2	-1.78	-2.63	-0.86 (-1.20, -0.52)‡	<0.001
Study 3	-1.05	-1.99	-0.94 (-1.38, -0.51)‡	<0.001
Eye Symptoms				
Study 1	-1.22	-1.47	-0.25 (-0.62, 0.11)	0.168
Study 2	-1.66	-2.06	-0.40 (-0.74, -0.06)	0.021
Study 3	-0.88	-1.62	-0.74 (-1.19, -0.30)‡	0.001
Emotional Problems				
Study 1	-1.11	-1.70	-0.59 (-0.96, -0.22)‡	0.002
Study 2	-1.49	-2.1	-0.61 (-0.93, -0.29)‡	<0.001
Study 3	-0.97	-1.51	-0.54 (-0.97, -0.12)‡	0.013
*entire treatment period †perceptions of impact of treatment rated on a 7-point scale (0=no impairment and 6=maximum impairment) ‡clinically meaningful improvement = absolute difference of ≥0.5 in the mean change from baseline over placebo CI = Confidence Interval; LS = Least Square				

Quality of Life Assessments in Patients Aged 12 and Older with Perennial Allergic Rhinitis (PAR)

The effect of *Veramyst* 110 mcg QD on quality of life in patients with PAR aged ≥12 years was evaluated in 2 multi-center, randomized, double-blind, placebo-controlled, parallel-group clinical trials. Study 1[23,77] and Study 2[29] were conducted over 4 weeks (N = 302) and 6 weeks (N = 302), respectively. Patients in both studies were symptomatic to appropriate perennial allergens including animal dander, house dust mites, cockroach, and/or mold.

In Study 1, patients who received *Veramyst* over 4 weeks experienced numerical improvements in overall RQLQ scores, and in 6 individual domains: activities, sleep, non-hay fever symptoms, practical problems, eye symptoms, and emotional problems compared with vehicle placebo (Table 38).[77] This improvement did not achieve statistical significance or a clinically meaningful improvement (absolute difference of ≥0.5 in the mean change from baseline over placebo). The seventh domain, nasal symptoms, achieved both statistical significance and a clinically meaningful improvement.

In Study 2, patients who received *Veramyst* over 6 weeks experienced a statistically significant improvement in overall RQLQ score and in all of the 7 individual domains compared with vehicle placebo (Table 38).[29] A clinically meaningful improvement was also observed for overall RQLQ scores as well as all individual domains except non-hay fever symptoms.

Table 38. Change from Baseline in RQLQ Scores in Adult and Adolescent Patients with PAR

Study 1 (Weeks 1-4)* Study 2 (Weeks 1-6)* Endpoint (Scale 0-6)†	**Vehicle Placebo (n = 153) (n = 151) LS Mean Change**	***Veramyst* 110 mcg QD (n = 149) (n = 151) LS Mean Change**	**LS Difference (95% CI)**	***P*- value**
RQLQ Overall				
Study 1	-1.18	-1.41	-0.23 (-0.59, 0.13)	0.214
Study 2	-1.20	-1.85	-0.65 (-0.90, -0.40)‡	<0.001
Activities				
Study 1	-1.30	-1.31	-0.01 (-0.50, 0.48)	0.960
Study 2	-1.51	-2.34	-0.83 (-1.22, -0.44)‡	<0.001
*entire treatment period †perceptions of impact of treatment rated on a 7-point scale (0=no impairment and 6=maximum impairment) ‡clinically meaningful improvement = absolute difference of ≥0.5 in the mean change from baseline CI = Confidence Interval; LS = Least Square				

Study 1 (Weeks 1-4)* Study 2 (Weeks 1-6)*	Vehicle Placebo (n = 153) (n = 151)	*Veramyst* 110 mcg QD (n = 149) (n = 151)		
Endpoint (Scale 0-6)†	**LS Mean Change**	**LS Mean Change**	**LS Difference (95% CI)**	***P*- value**
Sleep				
Study 1	-1.00	-1.06	-0.05 (-0.50, 0.40)	0.818
Study 2	-1.19	-1.74	-0.56 (-0.87, -0.25)‡	<0.001
Non-Nose/Eye Symptoms (non-hay fever)				
Study 1	-1.19	-1.28	-0.09 (-0.45, 0.27)	0.629
Study 2	-1.04	-1.49	-0.45 (-0.69, -0.21)	<0.001
Practical Problems				
Study 1	-1.41	-1.77	-0.36 (-0.79, 0.07)	0.101
Study 2	-1.51	-2.27	-0.77 (-1.10, -0.42)‡	<0.001
Nasal Symptoms				
Study 1	-1.17	-1.72	-0.55 (-0.99, -0.11)‡	0.015
Study 2	-1.41	-2.30	-0.88 (-1.19, -0.57)‡	<0.001
Eye Symptoms				
Study 1	-1.06	-1.16	-0.10 (-0.50, 0.29)	0.612
Study 2	-0.91	-1.46	-0.55 (-0.82, -0.28)‡	<0.001
Emotional Problems				
Study 1	-1.13	-1.46	-0.33 (-0.75, 0.09)	0.12
Study 2	-1.17	-1.85	-0.68 (-0.97, -0.39)‡	<0.001

*entire treatment period
†perceptions of impact of treatment rated on a 7-point scale (0=no impairment and 6=maximum impairment)
‡clinically meaningful improvement = absolute difference of ≥0.5 in the mean change from baseline
CI = Confidence Interval; LS = Least Square

10.2 Patients Preference for *Veramyst*

Patient Preference For Veramyst

Patients who participated in clinical studies for *Veramyst* completed a product characteristic questionnaire consisting of 6 subjective questions pertaining to their experience with the nasal spray device. The questions encompassed portability and acceptability of the device and perceptions regarding aftertaste, spray "run-off" following administration, and spray sensation. This questionnaire has not been validated but was used to gather data on the product.

Patient Preference for *Veramyst* in Seasonal Allergic Rhinitis (SAR)

Patients' experience with *Veramyst* Nasal Spray 110 mcg once daily (QD) in the morning was evaluated in 3, 2-week, double-blind, randomized, parallel-group, placebo controlled trials.[73,75,76] Studies 1 (N=299), 2 (N=285), and 3 (N=302) consisted of patients ≥12 years of age who had a diagnosis of SAR due to ragweed, grass pollen and mountain cedar, respectively. Results from the product characteristic questionnaire demonstrated that 91%-95% of patients with SAR found the nasal spray device to be somewhat easy to extremely easy to carry (Table 39). Eighty-two percent (82%) to 91% found the device to be somewhat easy to extremely easy to operate. The nasal spray nose tip was considered comfortable or extremely comfortable during administration of the spray by 93%-97% of patients. The mist generated by the device was rated as moderately to extremely gentle by 78%-93% of study participants. Approximately, one-third of patients reported no medication leakage out of the nose or down the throat. Most patients reported no aftertaste (52%-55%) or only a weak aftertaste (35%-36%) following administration of *Veramyst*.

Patient Preference for *Veramyst* in Perennial Allergic Rhinitis (PAR)

Patients' experience with *Veramyst* Nasal Spray was evaluated in a 4-week, double-blind, randomized, parallel-group, placebo-controlled study (N=302).[77] Patients ≥ 12 years of age with a diagnosis of PAR symptomatic to animal dander, house dust mites, cockroaches, and/or mold were randomized to treatment with *Veramyst* 110 mcg or vehicle placebo QD in the morning (4).

Product questionnaire results demonstrated that 94% of patients with PAR found the nasal spray device somewhat easy to extremely easy to carry (Table 39). Seventy-eight percent (78%) found the device to be somewhat easy to extremely easy to operate. The nasal spray nose tip was considered comfortable or extremely comfortable during administration of the spray by 95% of patients. The mist generated by the device was rated as moderately to extremely gentle by 90% of study participants. Thirty-eight percent (38%) of patients reported no medication leakage from the nose or down the throat. Approximately half of the patients (54%) reported no aftertaste or only a weak aftertaste (38%) following administration of *Veramyst*.

Table 39. Summary of Product Characteristic Questionnaire and Patient Preference for *Veramyst*

Characteristic	**SAR**			**PAR**
	Study 1 (N=299)	**Study 2 (N=285)**	**Study 3 (N=302)**	**Study 4 (N=302)**
	n (%)	**n (%)**	**n (%)**	**n (%)**
Ease in carrying the nasal spray				
Extremely easy	189 (63)	139 (49)	197 (65)	186 (62)
Somewhat easy	97 (32)	121 (42)	90 (30)	97 (32)
Somewhat difficult	6 (2)	23 (8)	13 (4)	13 (4)
Extremely difficult	3 (1)	0	1 (<1)	3 (<1)
Missing data	1 (<1)	---		2 (<1)
Ease in operating the nasal spray				
Extremely easy	184 (62)	111 (39)	168 (56)	132 (44)
Somewhat easy	87 (29)	122 (43)	85 (28)	104 (34)
Somewhat difficult	21 (7)	46 (16)	39 (13)	53 (18)
Extremely difficult	4 (1)	4 (1)	9 (3)	11 (4)
Missing data	---	---	---	1 (<1)
Comfort of the nasal spray nose tip				
Extremely comfortable	124 (41)	79 (28)	136 (45)	115 (38)
Comfortable	160 (54)	184 (65)	157 (52)	171 (57)
Uncomfortable	9 (3)	18 (6)	6 (2)	12 (4)
Extremely uncomfortable	3 (1)	2 (<1)	2 (<1)	2 (<1)
Missing data	---	---	---	1 (<1)
Gentleness of the nasal spray mist				
Extremely gentle	160 (54)	98 (34)	176 (58)	150 (50)
Moderately gentle	118 (39)	126 (44)	99 (33)	122 (40)
Slightly gentle	16 (5)	48 (17)	26 (9)	23 (8)
Not at all gentle	2 (<1)	11 (4)	0	5 (2)
Missing data	---	---	---	1 (<1)
Amount of nasal spray leaking out of nose or down throat				
None of the medication	87 (29)	127 (45)	102 (34)	116 (38)
Some of the medication	192 (64)	142 (50)	182 (60)	164 (54)
A lot of the medication	13 (4)	14 (5)	14 (5)	16 (5)
All of the medication	4 (1)	0	3 (<1)	4 (1)
Missing data	---	---	---	1 (<1)
Strength of aftertaste of the nasal spray				
No aftertaste	156 (52)	156 (55)	165 (55)	164 (54)
Weak aftertaste	107 (36)	99 (35)	107 (35)	114 (38)
Moderately strong aftertaste	30 (10)	27 (9)	26 (9)	22 (7)

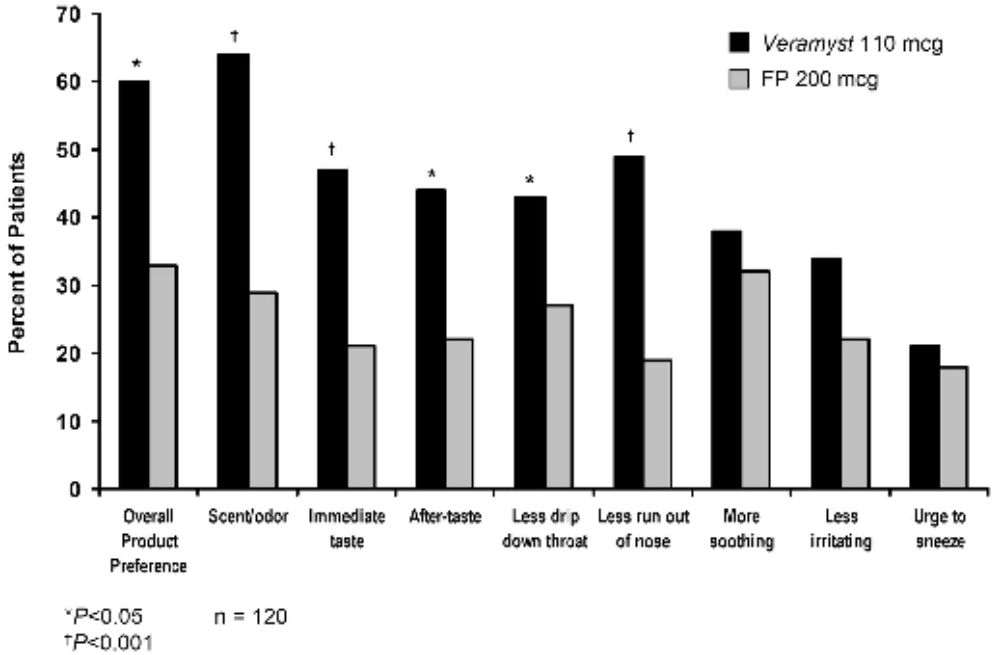
Characteristic	SAR			PAR
	Study 1 (N=299)	Study 2 (N=285)	Study 3 (N=302)	Study 4 (N=302)
	n (%)	n (%)	n (%)	n (%)
Extremely strong aftertaste	3 (1)	1 (<1)	3 (<1)	0
Missing data	---	---	---	1 (<1)

Patient Preference for Veramyst vs. Fluticasone Propionate Nasal Spray (FPNS)

Veramyst was compared with generic FPNS to identify patient preferences for selected product sensory attributes in a multicenter, double-blind, single-dose crossover study.[120] Patients ≥18 years of age with symptomatic seasonal and/or perennial allergic rhinitis (N=127) were randomized 1:1 to receive *Veramyst* 110 mcg followed by FPNS 200 mcg or FPNS followed by *Veramyst*. The primary measure was the overall preference for *Veramyst* or FPNS based on selected sensory attributes. Secondary measures were preferences for and subject ratings of individual sensory attributes. These attributes were assessed immediately after and 2 minutes after each single-dose treatment. At the end of crossover dosing and after completion of all attributes questionnaires, preference for individual attributes of *Veramyst* or FPNS as well as overall preference were evaluated in a third questionnaire. The 3 subject questionnaires were similar to those used previously to evaluate subjects' overall preference for therapy of allergic rhinitis.[121] Since the objective of this study involved subject-rated evaluation during and following crossover dosing, no efficacy data were collected. Therefore, the study outcomes are limited to health outcome endpoints.

A summary and analysis of attribute preference from 120 participants is presented in Figure 18. Overall, significantly more patients preferred *Veramyst* over FPNS (60% vs. 33%). Although 30% or more patients indicated no preference with regard to most sensory attributes, significantly more patients preferred *Veramyst* for scent/odor, immediate taste and aftertaste, less dripping down the throat, and less nose run-off.

Figure 18. Overall & Selected Product Attribute Preferences for *Veramyst* Compared with Generic Fluticasone Propionate Nasal Spray (FPNS)



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Appendix

Table 27. Change from Baseline in Primary and Secondary Endpoints

Endpoint*	Mean Change			LS Mean Difference (95% CI)			*P*-value		
Study 1 Study 2	Placebo (n=313) (n=229)	FEX (n=311) (n=227)	FFNS (n=312) (n=224)	FEX vs Placebo	FFNS vs Placebo	FFNS vs FEX	FEX vs Placebo	FFNS vs Placebo	FFNS vs FEX
NSS†									
	-1.9	-2.0	-2.9	0.0	-1.0	-0.9	0.816	<0.001	<0.001
				(-0.3,0.2)	(-1.2,-0.7)	(-1.2,-0.7)			
	-2.3	-2.2	-3.1	0.1	-0.8	-0.9	0.374	<0.001	<0.001
				-0.2,0.5	-1.1,-0.4	-1.2,-0.6			
N-rTNSS‡									
	-2.5	-2.7	-3.7	-0.3	-1.3	-1.0	0.136	<0.001	<0.001
				(-0.6,0.1)	(-1.6,-0.9)	(-1.4,-0.7)			
	-2.9	-2.9	-4.1	0.1	-1.2	-1.3	0.632	<0.001	<0.001
				-0.3,0.5	-1.6,-0.8	-1.7,-0.9			
D-rTNSS‡									
	-2.6	-3.0	-3.7	-0.3	-1.1	-0.8	0.136	<0.001	<0.001
				(-0.7,0.1)	(-1.5,-0.7)	(-1.2,-0.4)			
	-3.0	-2.9	-4.2	0.2	-1.2	-1.4	0.632	<0.001	<0.001
				-0.2,0.6	-1.6,-0.7	-1.8,-0.9			
24hr-rTNSS‡									
	-2.5	-2.8	-3.6	-0.3	-1.2	-0.9	0.136	<0.001	<0.001
				(-0.6,0.1)	(-1.6,-0.8)	(-1.3,-0.6)			
	-2.8	-2.8	-4.1	0.2	-1.2	-1.3	0.632	<0.001	<0.001
				-0.3,0.6	-1.6,-0.8	-1.7,-0.9			

* entire treatment period; † primary efficacy endpoint; ‡ key secondary endpoint; § other secondary endpoint

KEY: LS=Least Square; CI=Confidence Interval; FEX=fexofenadine; FFNS=fluticasone furoate nasal spray; NSS=nighttime symptoms score; TNSS=total nasal symptoms score; r=reflective; i=instantaneous; N=nighttime; D=daytime; TOSS=total ocular symptoms score; AM=morning; PM=evening; PNIF=peak nasal inspiratory flow; NRQLQ=nocturnal rhinoconjuntivitis quality of life questionnaire

Endpoint*	**Mean Change**			**LS Mean Difference (95% CI)**			***P*-value**		
Study 1 **Study 2**	**Placebo (n=313) (n=229)**	**FEX (n=311) (n=227)**	**FFNS (n=312) (n=224)**	**FEX vs Placebo**	**FFNS vs Placebo**	**FFNS vs FEX**	**FEX vs Placebo**	**FFNS vs Placebo**	**FFNS vs FEX**
Pre-dose iTNSS‡									
	-2.3	-2.6	-3.6	-0.2	-1.3	-1.1	0.193	<0.001	<0.001
				(-0.6,0.1)	(-1.7,-1.0)	(-1.4,-0.7)			
	-2.8	-2.7	-4.1	0.2	-1.3	-1.5	0.484	<0.001	<0.001
				-0.2,0.6	-1.7,-0.8	-1.9,-1.1			
N-rTOSS‡									
	-2.0	-2.2	-2.5	-0.2	-0.5	-0.3	0.286	0.001	0.106
				(-0.5,0.1)	(-0.8,-0.2)	(-0.6,0.0)			
	-2.3	-2.2	-2.7	0.1	-0.4	-0.6	0.400	0.034	0.002
				-0.2,0.5	-0.8,-0.1	-0.9,-0.2			
D-rTOSS‡									
	-2.2	-2.4	-2.6	-0.2	-0.4	-0.2	0.286	0.007	0.106
				(-0.5,0.1)	(-0.7,-0.1)	(-0.5,0.1)			
	-2.5	-2.4	-2.9	0.2	-0.4	-0.6	0.400	0.034	0.002
				-0.1,0.6	-0.7,-0.0	-0.9,-0.2			
24hr-rTOSS‡									
	-2.0	-2.2	-2.5	-0.2	-0.5	-0.3	0.286	0.003	0.106
				(-0.5,0.1)	(-0.7,-0.2)	(-0.6,0.0)			
	-2.3	-2.2	-2.7	0.2	-0.4	-0.5	0.400	0.034	0.002
				-0.2,0.5	-0.7,-0.1	-0.9,-0.2			
Pre-dose iTOSS‡									

* entire treatment period; † primary efficacy endpoint; ‡ key secondary endpoint; § other secondary endpoint
KEY: LS=Least Square; CI=Confidence Interval; FEX=fexofenadine; FFNS=fluticasone furoate nasal spray; NSS=nighttime symptoms score; TNSS=total nasal symptoms score; r=reflective; i=instantaneous; N=nighttime; D=daytime; TOSS=total ocular symptoms score; AM=morning; PM=evening; PNIF=peak nasal inspiratory flow; NRQLQ=nocturnal rhinoconjuntivitis quality of life questionnaire

Endpoint*	**Mean Change**			**LS Mean Difference (95% CI)**			***P*-value**		
Study 1 **Study 2**	**Placebo (n=313) (n=229)**	**FEX (n=311) (n=227)**	**FFNS (n=312) (n=224)**	**FEX vs Placebo**	**FFNS vs Placebo**	**FFNS vs FEX**	**FEX vs Placebo**	**FFNS vs Placebo**	**FFNS vs FEX**
	-1.9	-2.2	-2.4	-0.3	-0.5	-0.3	0.160	<0.001	0.058
				(-0.5,0.0)	(-0.8,-0.2)	(-0.6,0.0)			
	-2.2	-2.2	-2.7	0.1	-0.4	-0.6	0.484	0.014	0.002
				-0.2,0.5	-0.8,-0.1	-0.9,-0.2			
AM PNIF§									
	1.7	1.4	9.9	-0.4	8.4	8.8	0.779	<0.001	<0.001
				(-3.6,2.7)	(5.3,11.5)	(5.7,11.9)			
	4.8	2.2	13	-2.6	8	10.6	0.176	<0.001	<0.001
				-6.4,1.2	4.2,11.8	6.8,14.4			
PM PNIF§									
	0.2	1.3	7.1	0.7	7.0	6.3	0.662	<0.001	<0.001
				(-2.5,4.0)	(3.8,10.3)	(3.1,9.6)			
	2.3	0.3	9.7	-2.0	7.3	9.3	0.350	<0.001	<0.001
				-6.1,2.1	3.2,11.5	5.2,13.4			

* entire treatment period; † primary efficacy endpoint; ‡ key secondary endpoint; § other secondary endpoint
KEY: LS=Least Square; CI=Confidence Interval; FEX=fexofenadine; FFNS=fluticasone furoate nasal spray; NSS=nighttime symptoms score; TNSS=total nasal symptoms score; r=reflective; i=instantaneous; N=nighttime; D=daytime; TOSS=total ocular symptoms score; AM=morning; PM=evening; PNIF=peak nasal inspiratory flow; NRQLQ=nocturnal rhinoconjuntivitis quality of life questionnaire

Endpoint*	**Mean Change**			**LS Mean Difference (95% CI)**			***P*-value**		
Study 1 **Study 2**	**Placebo (n=313) (n=229)**	**FEX (n=311) (n=227)**	**FFNS (n=312) (n=224)**	**FEX vs Placebo**	**FFNS vs Placebo**	**FFNS vs FEX**	**FEX vs Placebo**	**FFNS vs Placebo**	**FFNS vs FEX**
NRQLQ§									
	-1.3	-1.5	-1.9	-0.1 (-0.4,0.1)	-0.6 (-0.8,-0.4)	-0.5 (-0.7,-0.3)	0.203	<0.001	<0.001
	-1.4	-1.4	-2.0	0.0 -0.2,0.3	-0.6 -0.9,-0.4	-0.7 -0.9,-0.4	0.791	<0.001	<0.001

* entire treatment period; † primary efficacy endpoint; ‡ key secondary endpoint; § other secondary endpoint
KEY: LS=Least Square; CI=Confidence Interval; FEX=fexofenadine; FFNS=fluticasone furoate nasal spray; NSS=nighttime symptoms score; TNSS=total nasal symptoms score; r=reflective; i=instantaneous; N=nighttime; D=daytime; TOSS=total ocular symptoms score; AM=morning; PM=evening; PNIF=peak nasal inspiratory flow; NRQLQ=nocturnal rhinoconjuntivitis quality of life questionnaire

Table 29. *Veramyst*: Clinical Summary Table for Seasonal Allergic Rhinitis in Adults and Adolescents

Citation	Duration	Design	Treatments/ SS	Inclusion/ Exclusion Criteria	Endpoints	Results
Kaiser et al[18]	2 weeks	MC, RDM, DB, PG, PBO-controlled Conducted at 17 U.S. sites during fall Ragweed season (Aug 05 – Oct 05)	FFNS 110 mcg/day [27.5 mcg/spray, 2 sprays each nostril every AM] (n=151) Vehicle PBO Nasal Spray (n=148) Total SS: 299	**Inclusion:** • Age ≥12 years • Diagnosis of SAR triggered by ragweed • Adequate exposure to ragweed pollen • Pts clinically symptomatic (average scores for rTNSS ≥6 & rTOSS ≥4) **Exclusion:** • Significant concomitant medical conditions, defined as but not limited to: Hx or current evidence of clinically significant uncontrolled disease of any body system; severe physical nasal obstruction or nasal septal perforation; nasal, ocular, or throat injury or surgery in the last 3 months; asthma; rhinitis medicamentosa; bacterial or viral infection of the eyes or upper respiratory tract within 2 weeks; acute or significant chronic sinusitis; current or hx of glaucoma and/or cataracts or ocular herpes simplex; clinical evidence of a *Candida* nasal infection; hx of any psychiatric disorder, or hx of adrenal insufficiency	**Primary:** • MCFB in daily rTNSS **Key Secondary:** • MCFB in AM pre-dose iTNSS • MCFB in daily rTOSS • ORT	**Efficacy:** FFNS significantly reduced nasal symptoms of SAR • LS mean treatment difference in daily rTNSS: -1.473 (95% CI -2.01, -0.94); $P<0.001$ • LS mean treatment difference in AM predose iTNSS: -1.375 (95% CI -1.90, -0.85); $P<0.001$ FFNS significantly reduced ocular symptoms of SAR • LS mean treatment difference in daily rTOSS: -0.600 (95% CI -1.01, -0.19); $P=0.004$ • Significant improvement in ORT (FFNS 20%, PBO 7%) • Moderate improvement in ORT (FFNS 22%, PBO 14%)

MC = Multi-center; RDM = randomized; DB = double-blind; PG = parallel-group; PBO = placebo; FFNS = fluticasone furoate nasal spray; AM = morning; SS = study subjects; SAR = seasonal allergic rhinitis; Pts = patients; TNSS = total nasal symptom score (sum of scores for rhinorrhea, nasal congestion, nasal itching and sneezing for a total score of up to a maximum of 12); rTNSS = reflective total nasal symptom score; TOSS = total ocular symptom score (sum of scores for itching/burning, tearing/watering, and redness for a total score of up to a maximum of 9); rTOSS = reflective total ocular symptom score; Hx = history; INS = intranasal steroid; MCFB = mean change from baseline over entire treatment period; iTNSS = instantaneous total nasal symptom score; ORT = overall response to therapy; LS = least square; CI = confidence interval; AEs = adverse events; FF = fluticasone furoate; PK = pharmacokinetic; concs = concentrations; HA = headache; ECG = elecrtocardiogram

Citation	Dura-tion	Design	Treatments/ SS	Inclusion/ Exclusion Criteria	Endpoints	Results
				• Systemic, inhaled or topical corticosteroid within 8 weeks • INS within 4 weeks • Use of other allergy medications within a specified time frame • Use of other medications that affect allergic rhinitis or its symptoms • Contact lenses or any ocular preparations		**Safety:** • Overall AEs (FFNS 21%, PBO 12%) • Most common AE: HA (FFNS 8%, PBO 3%) • Incidence of laboratory abnormalities low & similar between groups • Nasal examinations generally similar for the groups • Improved mucosal edema (FFNS 21%, PBO 17%) • Worsened mucosal bleeding (FFNS 4%, PBO <1%) • Changes in vital signs minor & similar between groups
MC = Multi-center; RDM = randomized; DB = double-blind; PG = parallel-group; PBO = placebo; FFNS = fluticasone furoate nasal spray; AM = morning; SS = study subjects; SAR = seasonal allergic rhinitis; Pts = patients; TNSS = total nasal symptom score (sum of scores for rhinorrhea, nasal congestion, nasal itching and sneezing for a total score of up to a maximum of 12); rTNSS = reflective total nasal symptom score; TOSS = total ocular symptom score (sum of scores for itching/burning, tearing/watering, and redness for a total score of up to a maximum of 9); rTOSS = reflective total ocular symptom score; Hx = history; INS = intranasal steroid; MCFB = mean change from baseline over entire treatment period; iTNSS = instantaneous total nasal symptom score; ORT = overall response to therapy; LS = least square; CI = confidence interval; AEs = adverse events; FF = fluticasone furoate; PK = pharmacokinetic; concs = concentrations; HA = headache; ECG = elecrtocardiogram						

Citation	Duration	Design	Treatments/ SS	Inclusion/ Exclusion Criteria	Endpoints	Results
Fokkens et al[20]	2 weeks	MC, RDM, DB, PG, PBO-controlled Conducted at 23 sites in 6 European countries during spring grass pollen season (May 05 – Aug 05)	FFNS 110 mcg/day [27.5 mcg/spray, 2 sprays each nostril every AM] (n=141) Vehicle PBO Nasal Spray (n=144) Total SS: 285	**Inclusion:** • Age ≥12 years • Diagnosis of SAR triggered by grass pollen • Adequate exposure to grass pollen • Pts clinically symptomatic (average scores for rTNSS ≥6 & rTOSS ≥4) **Exclusion:** • Significant concomitant medical conditions, defined as but not limited to: Hx or current evidence of clinically significant uncontrolled disease of any body system; severe physical nasal obstruction or nasal septal perforation; nasal, ocular, or throat injury or surgery in the last 3 months; asthma; rhinitis medicamentosa; bacterial or viral infection of the eyes or upper respiratory tract within 2 weeks; acute or significant chronic sinusitis; current or hx of glaucoma and/or cataracts or ocular herpes simplex; clinical evidence of a *Candida* nasal infection; hx of any psychiatric disorder	**Primary:** • MCFB in daily rTNSS **Key Secondary:** • MCFB in AM pre-dose iTNSS • MCFB daily rTOSS • ORT	**Efficacy:** FFNS significantly reduced nasal symptoms of SAR • LS mean treatment difference in daily rTNSS: -1.757 (95% CI -2.28, -1.23); $P<0.001$ • LS mean treatment difference in AM predose iTNSS: -1.898 (95% CI -2.42, -1.38); $P<0.001$ FFNS significantly reduced ocular symptoms of SAR • LS mean treatment difference in daily rTOSS: -0.741 (95% CI -1.14, -0.34); $P<0.001$ • Significant or moderate improvement in ORT (FFNS 67%, PBO 39%)

MC = Multi-center; RDM = randomized; DB = double-blind; PG = parallel-group; PBO = placebo; FFNS = fluticasone furoate nasal spray; AM = morning; SS = study subjects; SAR = seasonal allergic rhinitis; Pts = patients; TNSS = total nasal symptom score (sum of scores for rhinorrhea, nasal congestion, nasal itching and sneezing for a total score of up to a maximum of 12); rTNSS = reflective total nasal symptom score; TOSS = total ocular symptom score (sum of scores for itching/burning, tearing/watering, and redness for a total score of up to a maximum of 9); rTOSS = reflective total ocular symptom score; Hx = history; INS = intranasal steroid; MCFB = mean change from baseline over entire treatment period; iTNSS = instantaneous total nasal symptom score; ORT = overall response to therapy; LS = least square; CI = confidence interval; AEs = adverse events; FF = fluticasone furoate; PK = pharmacokinetic; concs = concentrations; HA = headache; ECG = elecrtocardiogram

Citation	Dura-tion	Design	Treatments/ SS	Inclusion/ Exclusion Criteria	Endpoints	Results
				• Systemic, inhaled or topical corticosteroid within 8 weeks • INS within 4 weeks • Use of other allergy medications within a specified time frame • Use of other medications that affect allergic rhinitis or its symptoms		**Safety:** • Overall AEs (FFNS 17%, PBO 16%) • Most common AE: HA (FFNS 9%, PBO 6%) • Most common drug-related AE: Epistaxis (FFNS 3%, PBO <1%) • Incidence of laboratory abnormalities low & similar between groups • FFNS improved mucosal edema & secretions vs. PBO • Nasal ulcers at week 2 (FFNS 4% , PBO 0%) • Changes in vital signs minor & similar between groups
MC = Multi-center; RDM = randomized; DB = double-blind; PG = parallel-group; PBO = placebo; FFNS = fluticasone furoate nasal spray; AM = morning; SS = study subjects; SAR = seasonal allergic rhinitis; Pts = patients; TNSS = total nasal symptom score (sum of scores for rhinorrhea, nasal congestion, nasal itching and sneezing for a total score of up to a maximum of 12); rTNSS = reflective total nasal symptom score; TOSS = total ocular symptom score (sum of scores for itching/burning, tearing/watering, and redness for a total score of up to a maximum of 9); rTOSS = reflective total ocular symptom score; Hx = history; INS = intranasal steroid; MCFB = mean change from baseline over entire treatment period; iTNSS = instantaneous total nasal symptom score; ORT = overall response to therapy; LS = least square; CI = confidence interval; AEs = adverse events; FF = fluticasone furoate; PK = pharmacokinetic; concs = concentrations; HA = headache; ECG = elecrtocardiogram						

Citation	Duration	Design	Treatments/ SS	Inclusion/ Exclusion Criteria	Endpoints	Results
Hampel et al[19]	2 weeks	MC, RDM, DB, PG, PBO-controlled Conducted at 7 sites in south-central Texas during mt. cedar season (Dec 04 – Jan 05)	FFNS 110 mcg/day [27.5 mcg/spray, 2 sprays each nostril every AM] (n=152) Vehicle PBO Nasal Spray (n=150) Total SS: 302	**Inclusion:** • Age ≥12 years • Diagnosis of SAR triggered by mt.cedar allergen • Adequate exposure to mt. cedar • Pts clinically symptomatic (average scores for rTNSS ≥6 & rTOSS ≥4) **Exclusion:** • Significant concomitant medical conditions, defined as but not limited to: Hx or current evidence of clinically significant uncontrolled disease of any body system; severe physical nasal obstruction or nasal septal perforation; nasal, ocular, or throat injury or surgery in the last 3 months; asthma; rhinitis medicamentosa; bacterial or viral infection of the eyes or upper respiratory tract within 2 weeks; acute or significant chronic sinusitis; current or hx of glaucoma and/or cataracts orocular herpes simplex; clinical evidence of a *Candida* nasal infection; hx of any psychiatric disorder	**Primary:** • MCFB in daily rTNSS **Key Secondary:** • MCFB in AM pre-dose iTNSS • MCFB in daily rTOSS • ORT	**Efficacy:** FFNS significantly reduced nasal symptoms of SAR • LS mean treatment difference in daily rTNSS: -0.777 (95% CI -1.28,-0.27); *P*=0.003 • LS mean treatment difference in AM predose iTNSS: -0.902 (95% CI -1.38,-0.42); *P*<0.001 FFNS significantly reduced ocular symptoms of SAR • LS mean treatment difference in daily rTOSS: -0.546 (95% CI -0.95,-0.14); *P*=0.008

MC = Multi-center; RDM = randomized; DB = double-blind; PG = parallel-group; PBO = placebo; FFNS = fluticasone furoate nasal spray; AM = morning; SS = study subjects; SAR = seasonal allergic rhinitis; Pts = patients; TNSS = total nasal symptom score (sum of scores for rhinorrhea, nasal congestion, nasal itching and sneezing for a total score of up to a maximum of 12); rTNSS = reflective total nasal symptom score; TOSS = total ocular symptom score (sum of scores for itching/burning, tearing/watering, and redness for a total score of up to a maximum of 9); rTOSS = reflective total ocular symptom score; Hx = history; INS = intranasal steroid; MCFB = mean change from baseline over entire treatment period; iTNSS = instantaneous total nasal symptom score; ORT = overall response to therapy; LS = least square; CI = confidence interval; AEs = adverse events; FF = fluticasone furoate; PK = pharmacokinetic; concs = concentrations; HA = headache; ECG = elecrtocardiogram

Citation	Dura-tion	Design	Treatments/ SS	Inclusion/ Exclusion Criteria	Endpoints	Results
				• Systemic, inhaled or topical corticosteroid within 8 weeks • INS within 4 weeks • Use of other allergy medications within a specified timeframe • Use of other medications that affect allergic rhinitis or its symptoms		• Significant & moderate improvement in ORT (FFNS 21% & 27%) vs. (PBO 11% & 20%) **Safety:** • Overall AEs (FFNS 22%, PBO 29%) • Most common AE: HA (FFNS 5%, PBO 4%) • Most common drug-related AE: Epistaxis (FFNS 3%, PBO 3%) • Incidence of laboratory abnormalities low & similar between groups • Nasal examinations generally similar for the groups • Changes in vital signs minor & similar between groups
MC = Multi-center; RDM = randomized; DB = double-blind; PG = parallel-group; PBO = placebo; FFNS = fluticasone furoate nasal spray; AM = morning; SS = study subjects; SAR = seasonal allergic rhinitis; Pts = patients; TNSS = total nasal symptom score (sum of scores for rhinorrhea, nasal congestion, nasal itching and sneezing for a total score of up to a maximum of 12); rTNSS = reflective total nasal symptom score; TOSS = total ocular symptom score (sum of scores for itching/burning, tearing/watering, and redness for a total score of up to a maximum of 9); rTOSS = reflective total ocular symptom score; Hx = history; INS = intranasal steroid; MCFB = mean change from baseline over entire treatment period; iTNSS = instantaneous total nasal symptom score; ORT = overall response to therapy; LS = least square; CI = confidence interval; AEs = adverse events; FF = fluticasone furoate; PK = pharmacokinetic; concs = concentrations; HA = headache; ECG = elecrtocardiogram						

Citation	Duration	Design	Treatments/ SS	Inclusion/ Exclusion Criteria	Endpoints	Results
Martin et al[118]	2 weeks	MC, RDM, DB, PG, PBO-controlled Conducted at 8 sites in south-central Texas during 2003-2004 mt. cedar season	FFNS 55 mcg/day (n=127) FFNS 110 mcg/day (n=127) FFNS 220 mcg/day (n=129) FFNS 440 mcg/day (n=130) Vehicle PBO Nasal Spray (n=128) Total SS: 641	**Inclusion:** • Age ≥12 years • Diagnosis of SAR triggered by mt. cedar allergen • Adequate exposure to mt. cedar • Pts clinically symptomatic & had 24-hour urine cortisol collection **Exclusion:** • Significant concomitant medical conditions, defined as but not limited to: Hx or current evidence of clinically significant uncontrolled disease of any body system; severe physical nasal obstruction; recent nasal septal surgery or nasal septal perforation; asthma; rhinitis medicamentosa; bacterial or viral infection of the upper respiratory tract within 2 weeks; acute or significant chronic sinusitis; current or hx of glaucoma and/or cataracts or ocular herpes simplex; clinical evidence of a *Candida* nasal infection or orpharynx; hx of any psychiatric disorder	**Primary:** • MCFB in daily rTNSS **Key Secondary:** • MCFB in AM pre-dose iTNSS • ORT **Other Secondary:** • FFNS systemic exposure	**Efficacy:** Significantly greater decreases in daily rTNSS for each FFNS dosage vs. PBO • LS mean difference vs. PBO: FFNS 55 mcg: -1.68 (95% CI -2.25, -1.10); $P<0.001$ FFNS 110 mcg: -2.01 (95% CI -2.58, -1.44); $P<0.001$ FFNS 220 mcg: -1.36 (95%CI -1.93, -0.79); $P<0.001$ FFNS 440 mcg: -2.19 (95% CI -2.75, -1.62); $P<0.001$ • Significantly greater decreases in AM iTNSS for each FFNS dosage vs. PBO • Moderately or significantly improved ORT: PBO (28%); 55 mcg (53%); 110 mcg (52%); 220 mcg (49%);440 mcg (59%)
MC = Multi-center; RDM = randomized; DB = double-blind; PG = parallel-group; PBO = placebo; FFNS = fluticasone furoate nasal spray; AM = morning; SS = study subjects; SAR = seasonal allergic rhinitis; Pts = patients; TNSS = total nasal symptom score (sum of scores for rhinorrhea, nasal congestion, nasal itching and sneezing for a total score of up to a maximum of 12); rTNSS = reflective total nasal symptom score; TOSS = total ocular symptom score (sum of scores for itching/burning, tearing/watering, and redness for a total score of up to a maximum of 9); rTOSS = reflective total ocular symptom score; Hx = history; INS = intranasal steroid; MCFB = mean change from baseline over entire treatment period; iTNSS = instantaneous total nasal symptom score; ORT = overall response to therapy; LS = least square; CI = confidence interval; AEs = adverse events; FF = fluticasone furoate; PK = pharmacokinetic; concs = concentrations; HA = headache; ECG = elecrtocardiogram						

Citation	Dura-tion	Design	Treatments/ SS	Inclusion/ Exclusion Criteria	Endpoints	Results
				• Systemic, inhaled or topical corticosteroid within 8 weeks • INS within 4 weeks • Use of other allergy medications within a specified timeframe • Use of other medications that affect allergic rhinitis or its symptoms		**Kinetics:** • FF PK analysis (1476 plasma samples/502 pts) • 78 (5.3% of total samples) had quantifiable concs in 59 pts (11.8% of pts) • Higher proportion of measurable concs as dose increased - majority of values being observed at highest dose • Plasma FF concs generally below limit of quantitation (10 pg/mL) for all FFNS dosages **Safety:** • Incidence of AEs comparable (24-29%) across all groups, including PBO • Most common AE: Epistaxis 4% (PBO), 3% (55 mcg), 8% (110 mcg), 9% (220 mcg), & 7% (440 mcg). All epistaxis events rated as mild. • No treatment related trends in vital signs • No ECG changes deemed clinically significant
MC = Multi-center; RDM = randomized; DB = double-blind; PG = parallel-group; PBO = placebo; FFNS = fluticasone furoate nasal spray; AM = morning; SS = study subjects; SAR = seasonal allergic rhinitis; Pts = patients; TNSS = total nasal symptom score (sum of scores for rhinorrhea, nasal congestion, nasal itching and sneezing for a total score of up to a maximum of 12); rTNSS = reflective total nasal symptom score; TOSS = total ocular symptom score (sum of scores for itching/burning, tearing/watering, and redness for a total score of up to a maximum of 9); rTOSS = reflective total ocular symptom score; Hx = history; INS = intranasal steroid; MCFB = mean change from baseline over entire treatment period; iTNSS = instantaneous total nasal symptom score; ORT = overall response to therapy; LS = least square; CI = confidence interval; AEs = adverse events; FF = fluticasone furoate; PK = pharmacokinetic; concs = concentrations; HA = headache; ECG = elecrtocardiogram						

Table 30. *Veramyst*: Clinical Summary Table for Perennial Allergic Rhinitis in Adults and Adolescents

Citation	Duration	Design	Treatments/ SS	Inclusion/ Exclusion Criteria	Endpoints	Results
Nathan et al[21]	4 weeks	MC, RDM, DB, PG PBO-controlled Conducted at 42 US sites & 5 Canadian sites (Jan 05 – May 05)	FFNS 110 mcg/day [27.5 mcg/spray, 2 sprays each nostril every AM] (n=149) Vehicle PBO Nasal Spray (n=153) Total SS: 302	**Inclusion:** ▪ Age ≥12 years ▪ Diagnosis of PAR ▪ Adequate exposure to animal dander, house dust mites, cockroach, and/or mold ▪ Pts clinically symptomatic during the 7-14 day screening period ▪ Pts required to have an average rTNSS ≥6	**Primary:** ▪ MCFB in daily rTNSS **Key Secondary:** ▪ MCFB in AM pre-dose, iTNSS ▪ ORT **Other Secondary:** ▪ MCFB in AM rTNSS ▪ MCFB in PM rTNSS ▪ MCFB in daily rTOSS ▪ MCFB in AM pre-dose iTOSS	**Efficacy:** FFNS more efficacious than PBO in ORT (*P*=0.005) FFNS significantly reduced nasal symptoms of PAR ▪ LS mean treatment difference in daily rTNSS: -0.71 (95% CI -1.20,-0.21); *P*=0.005 ▪ LS mean treatment difference in AM predose iTNSS: -0.71 (95% CI -1.20, -0.21); *P*=0.006 ▪ LS mean treatment difference in AM rTNSS: -0.74 (95% CI -1.24, -0.23); *P*=0.004

MC = Multicenter; RDM = randomized; DB = double-blind; PG = parallel-group; PBO = placebo; FFNS = fluticasone furoate nasal spray; AM = morning; SS = study subjects; PAR = perennial allergic rhinitis; Pts = patients; TNSS = total nasal symptom score (sum of scores for rhinorrhea, nasal congestion, nasal itching and sneezing for a total score of up to a maximum of 12); rTNSS = reflective total nasal symptom score; Hx = history; SAR = seasonal allergic rhinitis; INS = intranasal steroid; MCFB = mean change from baseline over entire treatment period; iTNSS = instantaneous total nasal symptom score; ORT = overall response to therapy; PM = evening; TOSS = total ocular symptom score (sum of scores for itching/burning, tearing/watering, and redness for a total score of up to a maximum of 9); rTOSS = reflective total ocular symptom score; iTOSS = instantaneous total ocular symptom score; LS = least square; CI = confidence interval; AEs=adverse events

Citation	Dura-tion	Design	Treatments/ SS	Inclusion/ Exclusion Criteria	Endpoints	Results
				Exclusion: ▪ Significant concomitant medical conditions, defined as but not limited to: Hx or current evidence of clinically significant uncontrolled disease of any body system; severe physical nasal obstruction or nasal septal perforation; nasal, ocular, or throat injury or surgery in the last 3 months; asthma (except very mild or mild/intermediate); rhinitis medicamentosa, bacterial or viral infection of the eyes or upper respiratory tract within 2 weeks; acute or significant chronic sinusitis; current or hx of glaucoma and/or cataracts or ocular herpes simplex; clinical evidence of a *Candida* infection of the nose or oropharynx; any psychiatric disorder, adrenal insufficiency; current chickenpox or measles infection or recent non-immune exposure; hx of shingles ▪ Diagnosis of SAR ▪ Systemic, inhaled, or topical corticosteroid within 8 weeks		▪ LS mean treatment difference in PM rTNSS: -0.66 (95% CI -1.17, -0.16); *P*=0.011 FFNS did not significantly reduce ocular symptoms of PAR ▪ LS mean treatment difference in daily rTOSS: -0.15 (95% CI -0.52, 0.22); *P*=0.428 ▪ LS mean treatment difference in AM pre-dose iTOSS: -0.24 (95% CI -0.63, 0.15); *P*=0.228
MC = Multicenter; RDM = randomized; DB = double-blind; PG = parallel-group; PBO = placebo; FFNS = fluticasone furoate nasal spray; AM = morning; SS = study subjects; PAR = perennial allergic rhinitis; Pts = patients; TNSS = total nasal symptom score (sum of scores for rhinorrhea, nasal congestion, nasal itching and sneezing for a total score of up to a maximum of 12); rTNSS = reflective total nasal symptom score; Hx = history; SAR = seasonal allergic rhinitis; INS = intranasal steroid; MCFB = mean change from baseline over entire treatment period; iTNSS = instantaneous total nasal symptom score; ORT = overall response to therapy; PM = evening; TOSS = total ocular symptom score (sum of scores for itching/burning, tearing/watering, and redness for a total score of up to a maximum of 9); rTOSS = reflective total ocular symptom score; iTOSS = instantaneous total ocular symptom score; LS = least square; CI = confidence interval; AEs=adverse events					

Citation	Dura-tion	Design	Treatments/ SS	Inclusion/ Exclusion Criteria	Endpoints	Results
				▪ INS within 4 weeks ▪ Use of other allergy medications within a specified timeframe ▪ Use of other medications that affect allergic rhinitis or its symptoms		**Safety:** ▪ Drug-related AEs (FFNS 19%, PBO 13%) ▪ Most common drug-related AE: Epistaxis (FFNS 8%, PBO 5%) ▪ Incidence of laboratory abnormalities low & similar between groups ▪ Changes in vital signs minor & similar between groups
MC = Multicenter; RDM = randomized; DB = double-blind; PG = parallel-group; PBO = placebo; FFNS = fluticasone furoate nasal spray; AM = morning; SS = study subjects; PAR = perennial allergic rhinitis; Pts = patients; TNSS = total nasal symptom score (sum of scores for rhinorrhea, nasal congestion, nasal itching and sneezing for a total score of up to a maximum of 12); rTNSS = reflective total nasal symptom score; Hx = history; SAR = seasonal allergic rhinitis; INS = intranasal steroid; MCFB = mean change from baseline over entire treatment period; iTNSS = instantaneous total nasal symptom score; ORT = overall response to therapy; PM = evening; TOSS = total ocular symptom score (sum of scores for itching/burning, tearing/watering, and redness for a total score of up to a maximum of 9); rTOSS = reflective total ocular symptom score; iTOSS = instantaneous total ocular symptom score; LS = least square; CI = confidence interval; AEs=adverse events						

Citation	Duration	Design	Treatments/ SS	Inclusion/ Exclusion Criteria	Endpoints	Results
Vasar et al[22]	6 weeks	MC, RDM, DB, PG PBO-controlled Conducted at 40 international sites, including 7 US (Feb 06 – Jun 06)	FFNS 110 mcg/day [27.5 mcg/spray, 2 sprays each nostril every AM] (n=151) Vehicle PBO Nasal Spray (n=151 Total SS: 302	**Inclusion:** ▪ Age ≥12 years ▪ Diagnosis of PAR ▪ Adequate exposure to animal dander, house dust mites, cockroach, and/or mold ▪ Pts clinically symptomatic during the 7-14 day screening period ▪ Pts required to have an average rTNSS ≥6 **Exclusion:** ▪ Significant concomitant medical conditions, defined as but not limited to: Hx or current evidence of clinically significant uncontrolled disease of any body system; severe physical nasal obstruction or nasal septal perforation; nasal or ocular injury or surgery in the last 3 months; asthma (very mild or mild/intermediate); rhinitis medicamentosa; bacterial or viral infection of the eyes or upper respiratory tract within 2 weeks; acute or significant chronic sinusitis; current or hx of glaucoma and/or cataracts or ocular herpes simplex;	**Primary:** ▪ MCFB in daily rTNSS **Key Secondary:** ▪ MCFB in AM pre-dose, iTNSS ▪ ORT **Other Secondary:** ▪ MCFB in AM rTNSS ▪ MCFB in PM rTNSS ▪ MCFB in daily rTOSS ▪ MCFB in AM pre-dose iTOSS	**Efficacy:** FFNS was more efficacious than PBO for ORT (P<0.001) FFNS significantly reduced nasal symptoms of PAR ▪ LS mean treatment difference in daily rTNSS: -1.26 (95% CI -1.73,-0.78); P<0.001 ▪ LS mean treatment difference in AM predose iTNSS: -1.5 (95% CI -1.93, -0.99); P<0.001 ▪ LS mean treatment difference in AM rTNSS: -1.27 (95% CI -1.74, -0.81); P<0.001 ▪ LS mean treatment difference in PM rTNSS: -1.29 (95% CI -1.77, -0.81); P<0.001

MC = Multicenter; RDM = randomized; DB = double-blind; PG = parallel-group; PBO = placebo; FFNS = fluticasone furoate nasal spray; AM = morning; SS = study subjects; PAR = perennial allergic rhinitis; Pts = patients; TNSS = total nasal symptom score (sum of scores for rhinorrhea, nasal congestion, nasal itching and sneezing for a total score of up to a maximum of 12); rTNSS = reflective total nasal symptom score; Hx = history; SAR = seasonal allergic rhinitis; INS = intranasal steroid; MCFB = mean change from baseline over entire treatment period; iTNSS = instantaneous total nasal symptom score; ORT = overall response to therapy; PM = evening; TOSS = total ocular symptom score (sum of scores for itching/burning, tearing/watering, and redness for a total score of up to a maximum of 9); rTOSS = reflective total ocular symptom score; iTOSS = instantaneous total ocular symptom score; LS = least square; CI = confidence interval; AEs=adverse events

Citation	Dura-tion	Design	Treatments/ SS	Inclusion/ Exclusion Criteria	Endpoints	Results
				clinical evidence of a *Candida* infection of the nose or oropharynx; any psychiatric disorder; adrenal insufficiency; current chickenpox or measles infection or recent non-immune exposure; hx of shingles ▪ Systemic, inhaled, or topical corticosteroid within 8 weeks ▪ INS within 4 weeks ▪ Use of other allergy medications within a specified timeframe ▪ Use of other medications that affect allergic rhinitis or its symptoms		FFNS significantly reduced the ocular symptoms of PAR ▪ LS mean treatment difference in daily rTOSS: -0.51 (95% CI -0.85, -0.16); *P*=0.004 ▪ LS mean treatment difference in AM pre-dose iTOSS: -0.49 (95% CI -0.85,-0.13); *P*=0.007 **Safety:** ▪ Drug-related AEs (FFNS 15%, PBO 11%) ▪ Most common drug-related AE: Epistaxis (FFNS 8%, PBO 4%) ▪ Incidence of laboratory abnormalities low & similar between groups ▪ Changes in vital signs minor & similar between groups
MC = Multicenter; RDM = randomized; DB = double-blind; PG = parallel-group; PBO = placebo; FFNS = fluticasone furoate nasal spray; AM = morning; SS = study subjects; PAR = perennial allergic rhinitis; Pts = patients; TNSS = total nasal symptom score (sum of scores for rhinorrhea, nasal congestion, nasal itching and sneezing for a total score of up to a maximum of 12); rTNSS = reflective total nasal symptom score; Hx = history; SAR = seasonal allergic rhinitis; INS = intranasal steroid; MCFB = mean change from baseline over entire treatment period; iTNSS = instantaneous total nasal symptom score; ORT = overall response to therapy; PM = evening; TOSS = total ocular symptom score (sum of scores for itching/burning, tearing/watering, and redness for a total score of up to a maximum of 9); rTOSS = reflective total ocular symptom score; iTOSS = instantaneous total ocular symptom score; LS = least square; CI = confidence interval; AEs=adverse events						

Table 31. *Veramyst*: Clinical Summary Table for Seasonal Allergic Rhinitis In Children

Citation	Duration	Design	Treatments/ SS	Inclusion/ Exclusion Criteria	Endpoints	Results
Meltzer et al[26] Data on File[78]	2 weeks	MC, RDM, DB, PG, PBO-controlled Conducted at 57 US sites (Mar 05 – Nov 05)	FFNS 55 mcg/day [27.5 mcg/spray, 1 spray each nostril every AM] (n=184) FFNS 110 mcg/day [27.5 mcg/spray, 2 sprays each nostril every AM] (n=184) Vehicle PBO Nasal Spray (n=186) Total SS: 554	**Inclusion:** • Age ≥2 and <12 years • Diagnosis of SAR • Adequate exposure to seasonal (spring/summer/fall) allergen prevalent to the geographic area • Pts clinically symptomatic during the screening period (rTNSS ≥6); ocular symptoms not a criteria for randomization **Exclusion:** • Significant concomitant medical conditions, defined as but not limited to: Hx or current evidence of clinically significant uncontrolled disease of any body system; severe physical obstruction of the nose or nasal septal perforation; nasal or ocular surgery in the last 3 months; asthma; rhinitis medicamentosa; bacterial or viral infection of the upper respiratory tract within 1 week; acute or significant chronic sinusitis; current or hx of glaucoma &/or cataracts or ocular herpes simplex; clinical evidence of a *Candida* infection of the nose or oropharynx; hx of adrenal insufficiency or adrenal disorders	**Primary:** • MCFB in rTNSS in pts 6 to <12 years **Key Secondary:** • MCFB iTNSS in pts 6 to <12 years • ORT in pts 6 to <12 years **Other Secondary:** • MCFB rTOSS in pts 6 to <12 years	**Disposition of Patients:** • Pts 6 to <12 years (n=448) • Pts 2 to <6 years (n=105) **Efficacy:** FFNS 110 mcg significantly reduced nasal symptoms of SAR • LS mean difference in rTNSS vs. PBO – Pts 6 to <12: -0.616 (*P*=0.025) – Pts 2 to <12: -0.609 (*P*=0.012) • LS mean difference in iTNSS vs. PBO – Pts 6 to <12: -0.668 (*P*=0.015) – Pts 2 to <12: -0.647 (*P*=0.008) • Significant ORT for FFNS 100 mcg vs. PBO (*P*<0.001) for both age groups • No significant difference for ocular endpoints; ocular endpoints at baseline were mild (3.8 to 4.4) No difference between FFNS 55 mcg & PBO for any primary or secondary endpoints

MC = Multi-center; RDM= randomized; DB = double-blind; PG = parallel-group; PBO = placebo; FFNS = fluticasone furoate nasal spray; AM = morning; SS = study subjects; SAR = seasonal allergic rhinitis; Pts = patients; TNSS = total nasal symptom score (sum of scores for rhinorrhea, nasal congestion, nasal itching and sneezing for a total score up to a maximum of 12); rTNSS = reflective total nasal symptom score; Hx = history; INS = intranasal steroid; MCFB = mean change from baseline; ; iTNSS = instantaneous total nasal symptom score; ORT = overall response to therapy; TOSS = total ocular symptom score (sum of scores for itching/burning, tearing/watering, and redness for a total score of up to a maximum of 9); rTOSS = reflective total ocular symptom score; LS = least square; AEs = adverse events; HA = headache

Citation	Duration	Design	Treatments/ SS	Inclusion/ Exclusion Criteria	Endpoints	Results
				• Systemic, inhaled, ocular or topical corticosteroid within 8 weeks • INS within 4 weeks • Use of other allergy medications within a specified timeframe • Use of other medications that affect allergic rhinitis or its symptoms		**Safety:** • Overall AEs: FFNS 55 mcg (30%); FFNS 110 mcg (30%); PBO (20%) • Most common AE: HA – FFNS 55 mcg (4%); FFNS 110 mcg (6%); PBO (4%) • Most common drug-related AE: Epistaxis – FFNS 55 mcg (3%); FFNS 110 mcg (2%); PBO (2%) • Incidence of laboratory abnormalities low & similar between groups • Nasal examinations generally similar between groups • Changes in vital signs minor & similar between groups
MC = Multi-center; RDM= randomized; DB = double-blind; PG = parallel-group; PBO = placebo; FFNS = fluticasone furoate nasal spray; AM = morning; SS = study subjects; SAR = seasonal allergic rhinitis; Pts = patients; TNSS = total nasal symptom score (sum of scores for rhinorrhea, nasal congestion, nasal itching and sneezing for a total score up to a maximum of 12); rTNSS = reflective total nasal symptom score; Hx = history; INS = intranasal steroid; MCFB = mean change from baseline; ; iTNSS = instantaneous total nasal symptom score; ORT = overall response to therapy; TOSS = total ocular symptom score (sum of scores for itching/burning, tearing/watering, and redness for a total score of up to a maximum of 9); rTOSS = reflective total ocular symptom score; LS = least square; AEs = adverse events; HA = headache						

Table 32. *Veramyst*: Clinical Summary Table for Perennial Allergic Rhinitis in Children

Citation	Duration	Design	Treatments/ SS	Inclusion/ Exclusion Criteria	Endpoints	Results
Maspero et al[27]	12 weeks	MC, RDM, DB, PG, PBO-controlled Multinational study in 61 sites in 7 countries (Feb 05 – Nov 05)	FFNS 55 mcg/day [27.5 mcg/spray, 1 spray each nostril every AM] (n=185) FFNS 110 mcg/day [27.5 mcg/spray, 2 sprays each nostril every AM] (n=185) Vehicle PBO Nasal Spray (n=188) Total SS: 558	**Inclusion:** • Age ≥2 and <12 years • Diagnosis of PAR • Adequate exposure to animal dander, house dust mites, cockroach, or mold • Pts clinically symptomatic during the screening period with a rTNSS ≥6 **Exclusion:** • Significant concomitant medical conditions, defined as but not limited to: Hx or current evidence of clinically significant uncontrolled disease of any body system; severe physical obstruction of the nose or nasal septal perforation; nasal or ocular surgery in the last 3 months; asthma; rhinitis medicamentosa; bacterial or viral infection of the eyes or upper respiratory tract within 1 week; acute or significant chronic sinusitis; current or hx of glaucoma and/or cataracts or ocular herpes simplex; clinical evidence of a *Candida* infection of the nose or oropharynx; hx of adrenal insufficiency or adrenal disorders	**Primary:** • MCFB over first 4 weeks in daily rTNSS in pts 6 to <12 years **Key Secondary:** • MCFB over the first 4 weeks in AM pre-dose iTNSS in pts 6 to <12 years • ORT over the first 4 weeks in pts 6 to <12 years	**Efficacy (Over Weeks 1-4):** FFNS significantly reduced nasal symptoms of PAR • LS mean difference in rTNSS vs. PBO (6 to <12 y.o.): – FFNS 55 mcg: -0.754 (*P*=0.003) – FFNS 110 mcg: -0.452 (*P*=0.073) • LS mean difference in rTNSS vs. PBO (2 to <12 y.o.): – FFNS 55 mcg: -0.812, (*P*<0.001) – FFNS 110 mcg: -0.475, (*P*=0.031) • LS mean difference in iTNSS vs. PBO (6 to <12 y.o.): – FFNS 55 mcg: -0.751 (*P*=0.002) – FFNS 110 mcg: -0.651 (*P*=0.009) • Only FFNS 55 mcg significant improvement in ORT vs, PBO – Pts 6 to <12 y.o. (*P*=0.024) – Pts 2 to <12 y.o.(*P*=0.002)

MC = Multicenter; RDM= randomized; DB = double-blind; PG = parallel-group; PBO = placebo; FFNS = fluticasone furoate nasal spray; AM = morning; SS = study subjects; PAR = perennial allergic rhinitis; Pts = patients; TNSS = total nasal symptom score (sum of scores for rhinorrhea, nasal congestion, nasal itching and sneezing for a total score up to a maximum of 12); rTNSS = reflective total nasal symptom score; Hx = history; INS = intranasal steroid; MCFB = mean change from baseline; iTNSS = instantaneous total nasal symptom score; ORT = overall response to therapy; LS = least square; AE(s) = adverse event(s); UC = urinary cortisol; popln = population; IOP = intraocular pressure; PSC(s) = posterior subcapsular cataract(s)

Citation	Duration	Design	Treatments/ SS	Inclusion/ Exclusion Criteria	Endpoints	Results
				• Hx of allergy to seasonal pollen that would be present in the geographical area • Systemic corticosteroids within 6 months • Inhaled, occular or topical corticosteroid within 8 weeks • INS within 4 weeks • Use of other allergy medications within a specified time frame • Use of other medications that affect allergic rhinitis or its symptoms		**Safety (Over Weeks 1-12)** • Overall AEs (FFNS 55 mcg 56%, FFNS 110 mcg 59%, PBO 59%) • Most common AE: Pharyngolaryngeal pain (FFNS 55 mcg 7%, FFNS 110 mcg 5%, PBO 7%) • Most common drug-related AE: Epistaxis (FFNS 55 mcg 4%, FFNS 110 mcg 3%, PBO 4%) • In UC popln (n=319), no pts in either FFNS or PBO with 24-hour UC excretion below the normal range at baseline or at endpoint • Incidence of laboratory abnormalities low and similar across groups • Nasal examinations generally similar for the groups • Changes in vital signs minor & similar across groups • Corneal & lens changes: ≤2% of pts across treatment groups • IOP ≥21mmHg at baseline or at Week 12: ≤1% of pts • Reports of cataracts over 12 weeks: (FFNS 55 mcg 4 pts , FFNS 110 mcg 0 pts, PBO 2 pts) • PSCs at Week 12 & reported as AEs (FFNS 55 mcg 1 pt, PBO 2 pts)

MC = Multicenter; RDM= randomized; DB = double-blind; PG = parallel-group; PBO = placebo; FFNS = fluticasone furoate nasal spray; AM = morning; SS = study subjects; PAR = perennial allergic rhinitis; Pts = patients; TNSS = total nasal symptom score (sum of scores for rhinorrhea, nasal congestion, nasal itching and sneezing for a total score up to a maximum of 12); rTNSS = reflective total nasal symptom score; Hx = history; INS = intranasal steroid; MCFB = mean change from baseline; iTNSS = instantaneous total nasal symptom score; ORT = overall response to therapy; LS = least square; AE(s) = adverse event(s); UC = urinary cortisol; popln = population; IOP = intraocular pressure; PSC(s) = posterior subcapsular cataract(s)

Table 33. *Veramyst*: Clinical Summary Table on Occurrence of Hypothalamic-Pituitary-Adrenal (HPA) Axis Effects

Citation	Duration	Design	Treatments/ SS	Inclusion/ Exclusion Criteria	Endpoints	Results
Patel et al[102]	6 weeks	RDM, DB, PG, PBO & Active-controlled Conducted at 1 US & 1 Canadian site (Jan 05 – May 05) Measurements of HPA axis function conducted during 24-hour domiciled visits at end of screening & treatment periods	FFNS 110 mcg/day x 6 weeks plus PBO capsules for last 7 days (n=48) Vehicle PBO Nasal Spray x 6 weeks plus PBO capsules for last 7 days (n=51) Vehicle PBO Nasal Spray x 6 weeks plus Prednisone 10 mg/day for last 7 days (n=13) UC Popln: 85 SC Popln: 99 Total SS: 112	**Inclusion:** • Age 12 to 65 years • Diagnosis of PAR with a ≥2 year hx & a (+) skin prick test to perennial allergen (animal dander, house dust mites, cockroaches, mold) • Pts required to have an average rTNSS ≥5 **Exclusion:** • Significant concomitant medical conditions, defined as but not limited to: Hx or current evidence of clinically significant uncontrolled disease of any body system; severe physical nasal obstruction; nasal injury or surgery in the last 3 months; asthma; rhinitis medicamentosa; bacterial or viral infection of upper respiratory tract within 1 week; acute or significant chronic sinusitis; current or history of glaucoma &/or cataracts or ocular herpes simplex; clinical evidence of a *Candida* infection of the nose or oropharynx; hx of any psychiatric disorder, or hx of adrenal insufficiency	**Primary:** • Change from baseline (expressed as a ratio) in 24-hour SC for the SC popln **Other Pharmacodynamic Study Endpoints** • Change from baseline in 24-hour free cortisol excretion & in total 24-hour urinary free cortisol excretion & 6-beta hydroxycortisol excretion	• Similar 24-hour SC results between FFNS & PBO: LS mean difference of -0.47 mcg/dL (95% CI -1.31, 0.37) • Significant 24-hour SC results between prednisone & PBO confirming the sensitivity of the model: LS mean difference of -4.57 mcg/dL (95% CI -5.83, -3.31) • Similar 24-hour UC results between FFNS & PBO: LS mean difference of 2.32 mcg/day (95% CI -6.76, 11.39) • No 24-hour UC data for prednisone-treated pts due to assay interference

MC = multi-center; RDM= randomized; DB = double blind; PG = parallel group; PBO = placebo; HPA = hypothalamic-pituitary-adrenal; FFNS = fluticasone furoate nasal spray; UC = urinary cortisol; Popln = population; SC = serum cortisol; SS = study subjects; PAR = perennial allergic rhinitis; Hx = history; pts = patients; TNSS = total nasal symptom score (sum of scores for rhinorrhea, nasal congestion, nasal itching and sneezing for up to a maximum total score of 12); rTNSS = reflective total nasal symptom score; INS = intranasal steroid; AM = morning; LS = least square; CI = confidence interval; MCFB = mean change from baseline

Citation	Duration	Design	Treatments/ SS	Inclusion/ Exclusion Criteria	Endpoints	Results
				• Systemic corticosteroid within 6 months • Inhaled or topical corticosteroids within 8 weeks • INS within 4 weeks • Use of other allergy medications within a specified timeframe • Use of other medications that affect allergic rhinitis or its symptoms • AM SC assessments outside the normal range (<2mcg/dL for pts 12 to 17 years; <5mcg/dL for pts 18 to 65 years)		

MC = multi-center; RDM= randomized; DB = double blind; PG = parallel group; PBO = placebo; HPA = hypothalamic-pituitary-adrenal; FFNS = fluticasone furoate nasal spray; UC = urinary cortisol; Popln = population; SC = serum cortisol; SS = study subjects; PAR = perennial allergic rhinitis; Hx = history; pts = patients; TNSS = total nasal symptom score (sum of scores for rhinorrhea, nasal congestion, nasal itching and sneezing for up to a maximum total score of 12); rTNSS = reflective total nasal symptom score; INS = intranasal steroid; AM = morning; LS = least square; CI = confidence interval; MCFB = mean change from baseline

Citation	Duration	Design	Treatments/ SS	Inclusion/ Exclusion Criteria	Endpoints	Results
Rosenblut et al[30]	52 weeks	MC, RDM, DB, PG, PBO, & Active-controlled Non-US, Multinational study in 75 sites in 13 countries (Sept 04 – Dec 05) Measurements of HPA axis function obtained from non-domiciled 24-hour UC collections before randomization & at weeks 12, 24 & 52	Randomization 3:1: FFNS 110 mcg/day (n=605) Vehicle PBO Nasal (n=201) Total SS: 806 UC Popln: 490	**Inclusion:** • Age ≥12 years • Diagnosis of PAR with a ≥2 year hx & a (+) skin prick test to perennial allergen (animal dander, house dust mites, cockroaches, mold) • Met the minimum symptom criterion during the screening period (rTNSS) ≥4) • Undergone 24-hour UC collection **Exclusion:** • Significant concomitant medical conditions, defined as but not limited to: Hx or current evidence of clinically significant uncontrolled disease of any body system; severe physical obstruction of the nose; nasal septal or facial surgery in the last 6 months; asthma (except mild intermittent); rhinitis medicamentosa; bacterial or viral infection of the upper respiratory tract within 2 weeks; acute or significant chronic sinusitis; current or hx of glaucoma &/or cataracts or ocular herpes simplex; clinical evidence of a *Candida* infection of the nose or oropharynx; hx of any psychiatric disorder, or hx of adrenal insufficiency	MCFB in 24-hour UC excretion for the UC popln	• Similar 24-hour UC results between FFNS & PBO: LS mean difference of 2.50 mcg/day (95% CI -5.49, 10.49) • No evidence for a decrease in 24-hour UC excretion following FFNS treatment for up to 1 year

MC = multi-center; RDM= randomized; DB = double blind; PG = parallel group; PBO = placebo; HPA = hypothalamic-pituitary-adrenal; FFNS = fluticasone furoate nasal spray; UC = urinary cortisol; Popln = population; SC = serum cortisol; SS = study subjects; PAR = perennial allergic rhinitis; Hx = history; pts = patients; TNSS = total nasal symptom score (sum of scores for rhinorrhea, nasal congestion, nasal itching and sneezing for up to a maximum total score of 12); rTNSS = reflective total nasal symptom score; INS = intranasal steroid; AM = morning; LS = least square; CI = confidence interval; MCFB = mean change from baseline

Citation	Duration	Design	Treatments/ SS	Inclusion/ Exclusion Criteria	Endpoints	Results
				• Systemic, inhaled or topical corticosteroid within 6 months • INS within 4 weeks • Use of other allergy medications within a specified timeframe • Use of other medications that affect allergic rhinitis or its symptoms		

MC = multi-center; RDM= randomized; DB = double blind; PG = parallel group; PBO = placebo; HPA = hypothalamic-pituitary-adrenal; FFNS = fluticasone furoate nasal spray; UC = urinary cortisol; Popln = population; SC = serum cortisol; SS = study subjects; PAR = perennial allergic rhinitis; Hx = history; pts = patients; TNSS = total nasal symptom score (sum of scores for rhinorrhea, nasal congestion, nasal itching and sneezing for up to a maximum total score of 12); rTNSS = reflective total nasal symptom score; INS = intranasal steroid; AM = morning; LS = least square; CI = confidence interval; MCFB = mean change from baseline

Citation	Duration	Design	Treatments/ SS	Inclusion/ Exclusion Criteria	Endpoints	Results
Ratner et al[104]	6 weeks	MC, RDM, DB, PG, PBO-controlled Conducted at 10 US sites (Feb 05 – Jun 05) Measurements of HPA axis function conducted during 24-hour domiciled visits at end of screening & treatment periods	FFNS 110 mcg/day (n=57) Vehicle PBO Nasal Spray (n=55) UC Popln: 84 SC Popln: 101 Total SS: 112	**Inclusion:** • Age 2 to <12 years • Diagnosis of PAR with a ≥1 year hx (pts 4 to <12 years) or 6 month hx (pts 2 to <4 years) & a (+) skin prick test to perennial allergen (animal dander, house dust mites, cockroaches, mold) • Pts required to have an average rTNSS ≥5 **Exclusion:** • Significant concomitant medical conditions, defined as but not limited to: Hx or current evidence of clinically significant uncontrolled disease of any body system; severe physical nasal obstruction; nasal injury or surgery in the last 3 months; asthma; rhinitis medicamentosa; bacterial or viral infection of upper respiratory tract within 1 week; acute or significant chronic sinusitis; current or hx of glaucoma &/or cataracts or ocular herpes simplex; clinical evidence of a *Candida* infection of the nose or oropharynx; hx of any psychiatric disorder, or hx of adrenal insufficiency	**Primary:** • Change from baseline (expressed as a ratio) in 24-hour SC for the SC popl **Other Pharmacodynamic Study Endpoints** • Change from baseline in 24-hour free cortisol excretion & in total 24-hour urinary free cortisol excretion & 6-beta hydroxycortisol excretion	• Similar 24-hour SC results between FFNS & PBO: LS mean difference of -0.11 mcg/dL (95% CI -0.88, 0.66) • Similar 24-hour UC results between FFNS & PBO: LS mean difference of -1.43 mcg/day (95% CI -5.21, 2.35)
MC = multi-center; RDM= randomized; DB = double blind; PG = parallel group; PBO = placebo; HPA = hypothalamic-pituitary-adrenal; FFNS = fluticasone furoate nasal spray; UC = urinary cortisol; Popln = population; SC = serum cortisol; SS = study subjects; PAR = perennial allergic rhinitis; Hx = history; pts = patients; TNSS = total nasal symptom score (sum of scores for rhinorrhea, nasal congestion, nasal itching and sneezing for up to a maximum total score of 12); rTNSS = reflective total nasal symptom score; INS = intranasal steroid; AM = morning; LS = least square; CI = confidence interval; MCFB = mean change from baseline						

Citation	Duration	Design	Treatments/ SS	Inclusion/ Exclusion Criteria	Endpoints	Results
				• Systemic corticosteroid within 6 months • Inhaled or topical corticosteroids within 8 weeks • INS within 4 weeks • Use of other allergy medications within a specified timeframe • Use of other medications that affect allergic rhinitis or its symptoms • AM SC assessment outside the normal range (<2mcg/dL)		
MC = multi-center; RDM= randomized; DB = double blind; PG = parallel group; PBO = placebo; HPA = hypothalamic-pituitary-adrenal; FFNS = fluticasone furoate nasal spray; UC = urinary cortisol; Popln = population; SC = serum cortisol; SS = study subjects; PAR = perennial allergic rhinitis; Hx = history; pts = patients; TNSS = total nasal symptom score (sum of scores for rhinorrhea, nasal congestion, nasal itching and sneezing for up to a maximum total score of 12); rTNSS = reflective total nasal symptom score; INS = intranasal steroid; AM = morning; LS = least square; CI = confidence interval; MCFB = mean change from baseline						

Citation	Duration	Design	Treatments/ SS	Inclusion/ Exclusion Criteria	Endpoints	Results
Maspero et al[27]	12 weeks	MC, RDM, DB, PG, PBO-controlled Multinational study in 61 sites in 7 countries (Feb 05 – Nov 05) Measurements of HPA axis function obtained from non-domiciled 24-hour UC collections at randomization & final treatment visits	FFNS 55 mcg/day [27.5 mcg/spray, 1 spray each nostril every AM] (n=185) FFNS 110 mcg/day [27.5 mcg/spray, 2 sprays each nostril every AM] (n=185) Vehicle PBO Nasal Spray (n=188) Total SS: 558 UC Popln: FFNS 55 mcg (n=109), FFNS 110 mcg (n=103), PBO (n=107)	**Inclusion:** • Age 2 to <12 years • Diagnosis of PAR with a ≥1 year hx (pts 4 to <12 years) or 6 month hx (pts 2 to <4 years) & a (+) skin prick test to perennial allergen (animal dander, house dust mites, cockroaches, mold) • Pts required to have an average rTNSS ≥6 **Exclusion:** • Significant concomitant medical conditions, defined as but not limited to: Hx or current evidence of clinically significant uncontrolled disease of any body system; severe physical nasal obstruction; nasal injury or surgery in the last 3 months; asthma; rhinitis medicamentosa; bacterial or viral infection of upper respiratory tract within 1 week; acute or significant chronic sinusitis; current or hx of glaucoma &/or cataracts or ocular herpes simplex; clinical evidence of a *Candida* infection of the nose or oropharynx; hx of any psychiatric disorder, or hx of adrenal insufficiency • Systemic corticosteroid within 6 months • Inhaled or topical corticosteroids within 8 weeks	Change from baseline in 24-hour urinary free cortisol excretion in UC popln (pts 6 to 11 years)	• Similar 24-hour UC results between FFNS 55 mcg & PBO: LS mean difference of -3.01 mcg/day (95% CI -6.16, 0.13) • Similar 24-hour UC results between FFNS 110 mcg & PBO: LS mean difference of -2.14 mcg/day (95% CI -5.33, 1.04) • No patient with 24-hour UC excretion below normal range at anytime during study

MC = multi-center; RDM= randomized; DB = double blind; PG = parallel group; PBO = placebo; HPA = hypothalamic-pituitary-adrenal; FFNS = fluticasone furoate nasal spray; UC = urinary cortisol; Popln = population; SC = serum cortisol; SS = study subjects; PAR = perennial allergic rhinitis; Hx = history; pts = patients; TNSS = total nasal symptom score (sum of scores for rhinorrhea, nasal congestion, nasal itching and sneezing for up to a maximum total score of 12); rTNSS = reflective total nasal symptom score; INS = intranasal steroid; AM = morning; LS = least square; CI = confidence interval; MCFB = mean change from baseline

Citation	Duration	Design	Treatments/ SS	Inclusion/ Exclusion Criteria	Endpoints	Results
				• INS within 4 weeks • Use of other allergy medications within a specified timeframe • Use of other medications that affect allergic rhinitis or its symptoms		
MC = multi-center; RDM= randomized; DB = double blind; PG = parallel group; PBO = placebo; HPA = hypothalamic-pituitary-adrenal; FFNS = fluticasone furoate nasal spray; UC = urinary cortisol; Popln = population; SC = serum cortisol; SS = study subjects; PAR = perennial allergic rhinitis; Hx = history; pts = patients; TNSS = total nasal symptom score (sum of scores for rhinorrhea, nasal congestion, nasal itching and sneezing for up to a maximum total score of 12); rTNSS = reflective total nasal symptom score; INS = intranasal steroid; AM = morning; LS = least square; CI = confidence interval; MCFB = mean change from baseline						

Table 34. *Veramyst*: Clinical Summary Table of Long-Term Safety

Citation	Duration	Design	Treatments/ SS	Inclusion/ Exclusion Criteria	Endpoints	Results
Rosenblut et al[30] Data on File[31]	52 Weeks	MC, RDM, DB, PG, PBO & Active-controlled Non-US, Multinational study in 75 sites in 13 countries (Sept 04 – Dec 05)	Randomization 3:1 FFNS 110 mcg/day (n=605) Vehicle PBO Nasal (n=201) Total SS: 806 UC Popln: 490	**Inclusion:** • Age ≥12 years • Diagnosis of PAR with a ≥2 year hx & a (+) skin prick test to perennial allergen (animal dander, house dust mites, cockroaches, mold) • Met minimum symptom criterion during screening period (rTNSS ≥4) • Undergone 24-hour UC collection • Ophth exam within normal limits **Exclusion:** • Significant concomitant medical conditions, defined as but not limited to: Hx or current evidence of clinically significant uncontrolled disease of any body system; severe physical obstruction of the nose; nasal septal or facial cosmetic surgery in the last 6 months; asthma; rhinitis medicamentosa; bacterial or viral infection of the upper respiratory tract within 2 weeks; acute or significant chronic sinusitis; current or hx of glaucoma &/or cataracts or ocular herpes simplex; clinical evidence of a *Candida* infection of the nose or oropharynx; hx of any psychiatric disorder, or hx of adrenal insufficiency	**Safety Endpoints:** • AEs • Routine lab tests • ECG assessment • Vital signs • Nasal exams • MCFB in 24-hour UC excretion for the UC popln • Slit-lamp & funduscopic exams • Evaluation for glaucoma & changes in IOP	**Overall Safety:** • Overall AEs (FFNS 77%, PBO 71%) • Most common AE: Epistaxis, majority rated mild (FFNS 20%, PBO 8%) • Incidence of lab abnormalities low & similar between groups • 1 pt in each group with unfavorable, non-drug related ECG change • Changes in vital signs minor & similar between groups • Mucosal crusting & mucosal bleeding seen in higher % of FFNS-treated pts than PBO; proportions did not increase with increased treatment duration • Worsening nasal ulcers (FFNS ≤6%, PBO ≤3%) **UC Excretion** • Similar 24-hour UC results between FFNS & PBO: LS mean difference of 2.50 mcg/day (95% CI -5.49, 10.49) • No evidence for a decrease in 24-hour UC excretion following treatment with FFNS for up to 1 year

MC = multi-center; RDM = randomized; DB = double blind; PG = parallel group; PBO = placebo; FFNS = fluticasone furoate nasal spray; SS = study subjects; UC = urinary cortisol; Popln = population; PAR = perennial allergic rhinitis; Hx = history; TNSS = total nasal symptom score (sum of scores for rhinorrhea, nasal congestion, nasal itching and sneezing for a total score of up to a maximum of 12); rTNSS = reflective total nasal symptom score; INS = intranasal steroid; AE(s) = adverse event(s); ECG = electrocardiogram; MCFB = mean change from baseline; IOP = intraocular pressure; pt(s) = patient(s); PSC(s) = posterior subcapsular cataract(s)

Citation	Dura-tion	Design	Treat-ments/ SS	Inclusion/ Exclusion Criteria	Endpoints	Results
				• Systemic, inhaled or topical corticosteroid within 6 months • INS within 4 weeks • Use of other allergy medications within a specified time frame • Use of other medications that affect allergic rhinitis or its symptoms		**Ophth Evaluations** • No changes in most funduscopic & slit lamp exams; any changes seen were similar in treatment groups • Cataracts not present at baseline & identified during ophth exams (FFNS 6 pts , PBO 1 pt) • PSCs not present at baseline & reported as AEs [FFNS 2 pts (<1%), PBO 1 pt (<1%)]; PSC not detected in post-study evaluation in an FFNS-treated pt. • ≥98% of pts with no shift from baseline in IOP at any time in the study; 12 FFNS-treated pts (2%) had changes to at least 21 mmHg during the study; of these 12 pts, all but one had values of 21 or 22 mmHg; no pt had a value ≥21 mmHg for ≥1 treatment visit
MC = multi-center; RDM = randomized; DB = double blind; PG = parallel group; PBO = placebo; FFNS = fluticasone furoate nasal spray; SS = study subjects; UC = urinary cortisol; Popln = population; PAR = perennial allergic rhinitis; Hx = history; TNSS = total nasal symptom score (sum of scores for rhinorrhea, nasal congestion, nasal itching and sneezing for a total score of up to a maximum of 12); rTNSS = reflective total nasal symptom score; INS = intranasal steroid; AE(s) = adverse event(s); ECG = electrocardiogram; MCFB = mean change from baseline; IOP = intraocular pressure; pt(s) = patient(s); PSC(s) = posterior subcapsular cataract(s)						

Table 35. *Veramyst*: Clinical Summary Table Comparison with Fluticasone Propionate Nasal Spray

Citation	Duration	Design	Treatment/ SS	Inclusion/ Exclusion Criteria	Endpoints	Results
Data on File (107)	2 weeks	MC, RDM, DB, PG, PBO-controlled trial, to demonstrate non-inferiority of FFNS vs FPNS Conducted at 7 sites in Japan (Feb 05 – April 05)	FFNS 110 mcg QD (n=147) FFNS PBO (n=70) FPNS 100 mcg BID (n=144) FPNS PBO (n=72) Total SS: 446	**Inclusion**: • Age ≥16 years • Hx of SAR (cedar pollinosis) for at least 2 years • (+) allergy tests • Score of ≥4 on 3TNSS **Exclusion:** • Travel outside geographical region for at least 48 hours where exposure to pollens expected during the screening & treatment periods	**Primary:** • MCFB over 2 weeks in 3TNSS **Key Secondary:** • MCFB over 2 weeks in 4TNSS • MCFB over Week 1 and Week 2 in 3TNSS & 4TNSS • Mean % change from baseline over 2 weeks in 3TNSS & 4TNSS • MCFB over 2 weeks, Week 1 & Week 2 in individual nasal symptom scores	**Efficacy:** • MCFB over 2 weeks between treatments in 3TNSS: -0.173 (95% CI -0.51, 0.17) • Upper limit of the CI lower than the non-inferiority margin of 0.75, demonstrating that FFNS was non-inferior to FPNS • Secondary endpoints not evaluated for statistical significance between FFNS & FPNS • Statistically significant improvements in all secondary endpoints for FFNS vs. FFNS PBO

MC = Multi-center; RDM= randomized; DB = double-blind; PG = parallel-group; PBO = placebo; FFNS = fluticasone furoate nasal spray; FPNS = fluticasone propionate nasal spray; PBO = placebo; QD = daily; BID = twice a day; SS = study subjects; Hx = history; SAR = seasonal allergic rhinitis; MCFB = mean change from baseline; 3TNSS = total nasal symptom score (sum of scores for sneezing, rhinorrhea, and nasal congestion for a total score up to a maximum of 9); 4TNSS = total nasal symptom score (sum of scores for sneezing, rhinorrhea, nasal congestion, and nasal itching for a total score up to a maximum of 12); CI = confidence interval; AEs = adverse events; WBC = white blood cell; SC = serum cortisol

Citation	Duration	Design	Treatment/ SS	Inclusion/ Exclusion Criteria	Endpoints	Results
				• Complications or use of medications or therapies that might affect evaluation	• Change from baseline at Week 1 & Week 2 or Early Withdrawal in the score of individual nasal findings (swelling of inferior turbinate mucosa, color of inferior turbinate mucosa, watery secretion volume & nature of rhinorrhea, under rhinoscopy)	**Safety:** AEs ≥1% for active treatments • ↑WBC (FFNS 1%; FPNS <1%) • Epistaxis (FFNS 0%; FPNS 1%) • AEs reported for FFNS & FFNS PBO similar in nature & incidence • No significant difference in the MCFB in SC in any treatment group at week 2 or early withdrawal
MC = Multi-center; RDM= randomized; DB = double-blind; PG = parallel-group; PBO = placebo; FFNS = fluticasone furoate nasal spray; FPNS = fluticasone propionate nasal spray; PBO = placebo; QD = daily; BID = twice a day; SS = study subjects; Hx = history; SAR = seasonal allergic rhinitis; MCFB = mean change from baseline; 3TNSS = total nasal symptom score (sum of scores for sneezing, rhinorrhea, and nasal congestion for a total score up to a maximum of 9); 4TNSS = total nasal symptom score (sum of scores for sneezing, rhinorrhea, nasal congestion, and nasal itching for a total score up to a maximum of 12); CI = confidence interval; AEs = adverse events; WBC = white blood cell; SC = serum cortisol						

Table 36. *Veramyst*: Clinical Summary Table Comparison with Fexofenadine

Citation	Duration	Design	Treatment/ SS	Inclusion/ Exclusion Criteria	Endpoints	Results
Data on File (108)	2 week	MC, RDM, DB, PG, DD, PBO-controlled Conducted at 10 US sites (Dec 06 – Feb 07)	FFNS 110 mcg & oral PBO capsule QD (n=312) FEX 180 mg capsule & vehicle-PBO nasal spray QD (n=311) vehicle-PBO nasal spray & oral PBO capsule QD (n=313) Total SS: 936	**Inclusion:** • Age ≥12 years & resident of south-central Texas • Hx of SAR to mt. cedar with a ≥2 year diagnosis • (+) mt. cedar skin prick test • Pts clinically symptomatic during screening period: NSS ≥4.5, congestion on awakening ≥2, D-rTNSS ≥6, reflective nasal congestion ≥2, D-rTOSS ≥4, & diary completion >80%. **Exclusion:**• Significant concomitant medical conditions, defined as but not limited to: Hx or current evidence of clinically significant uncontrolled disease of any body system; severe physical obstruction of the nose or nasal septal perforation; nasal or ocular injury/surgery within 3 months; asthma except mild intermittent; rhinitis medicamentosa; bacterial or viral infection of the eyes or upper respiratory tract within 2 weeks; acute or significant chronic sinusitis; current or hx of glaucoma &/or cataracts or ocular herpes simplex; clinical evidence of a nasal *Candida* infection;	**Primary:** • MCFB in NSS **Key Secondary:**• MCFB in 24hr-rTNSS, D-rTNSS, N-rTNSS, pre-dose iTNSS • MCFB in 24hr-rTOSS, D-rTOSS, N-rTOSS, pre-dose iTOSS **Other Secondary:** • MCFB for NRQLQ • MCFB in AM & PM PNIF	**Results:** • FFNS significantly greater improvements in NSS, 24hr-rTNSS, D-rTNSS, N-rTNSS, & pre-dose iTNSS vs. FEX & vs. PBO (P <0.001) • No statistical difference between FFNS & FEX for improvement in ocular symptoms • FFNS significantly greater improvements in 24hr-rTOSS, D-rTOSS, N-rTOSS, & pre-dose iTOSS vs, PBO (P≤0.007) • FFNS significantly greater improvements in NRQLQ (global score) vs. FEX & vs. PBO (P<0.001) • FFNS significantly greater improvements in AM & PM PNIF vs. FEX & vs. PBO (P<0.001) **Safety:** • AEs similar in nature & incidence for FFNS, FEX & PBO

MC = Multi-center; RDM= randomized; DB = double-blind; PG = parallel-group; DD = double dummy; PBO = placebo; FFNS = fluticasone furoate nasal spray; QD = daily; FEX = fexofenadine; SS = study subjects; Hx = history; SAR = seasonal allergic rhinitis; pts = patients; NSS = nighttime symptom score (sum of scores for 3 questions relating to nasal congestion on awakening, nighttime awakenings due to nasal symptoms & degree of difficulty going to sleep due to nasal symptoms for a total score up to a maximum of 9); TNSS = total nasal symptom score (sum of scores for rhinorrhea, nasal congestion, nasal itching & sneezing for a total score up to a maximum of 12); D-rTNSS = daytime reflective total nasal symptom score; N-rTNSS = nighttime reflective total nasal symptom score; 24hr-rTNSS = average of D-rTNSS & N-rTNSS; iTNSS = instantaneous total nasal symptom score; TOSS = total ocular symptom score (sum of scores for itching/burning, tearing/watering, & redness for a total score up to a maximum of 9); D-rTOSS = daytime reflective total ocular symptom score; N-rTOSS = nighttime reflective total ocular symptom score; 24hr-rTOSS = average of D-rTOSS & N-rTOSS; iTOSS = instantaneous total ocular symptom score; INS = intranasal steroid spray; MCFB = mean change from baseline over entire treatment period; NRQLQ = nocturnal rhinoconjunctivitis quality of life questionnaire (16-items assessing 4 domains individually & globally (sleep problems, sleep time problems, symptoms on awaking in morning & practical problems); AM = morning (prior to taking dose); PM = evening; PNIF = peak nasal inspiratory flow; AEs = adverse events; HA = headache

Citation	Duration	Design	Treatment/ SS	Inclusion/ Exclusion Criteria	Endpoints	Results
				hx of any psychiatric disorder or other conditions that would limit or confound interpretation of study results; hx of renal impairment, sleep disorders, or Hepatitis B or C • Systemic, inhaled, ocular, or topical corticosteroid within 8 weeks • INS within 4 weeks • Use of other allergy medications within a specified timeframe • Use of other medications that affect the study medications, allergic rhinitis or its symptoms		• Most common AEs for FFNS: HA (4%), epistaxis (2%), pharyngolaryngeal pain (2%), pyrexia (<1%) • Most common AEs for FEX: HA (3%), epistaxis (<1%), pharyngolaryngeal pain (<1%), pyrexia (1%) • Most common AEs for PBO: HA (4%), epistaxis (2%), pharyngolaryngeal pain (1%), pyrexia (<1%)

MC = Multi-center; RDM= randomized; DB = double-blind; PG = parallel-group; DD = double dummy; PBO = placebo; FFNS = fluticasone furoate nasal spray; QD = daily; FEX = fexofenadine; SS = study subjects; Hx = history; SAR = seasonal allergic rhinitis; pts = patients; NSS = nighttime symptom score (sum of scores for 3 questions relating to nasal congestion on awakening, nighttime awakenings due to nasal symptoms & degree of difficulty going to sleep due to nasal symptoms for a total score up to a maximum of 9); TNSS = total nasal symptom score (sum of scores for rhinorrhea, nasal congestion, nasal itching & sneezing for a total score up to a maximum of 12); D-rTNSS = daytime reflective total nasal symptom score; N-rTNSS = nighttime reflective total nasal symptom score; 24hr-rTNSS = average of D-rTNSS & N-rTNSS; iTNSS = instantaneous total nasal symptom score; TOSS = total ocular symptom score (sum of scores for itching/burning, tearing/watering, & redness for a total score up to a maximum of 9); D-rTOSS = daytime reflective total ocular symptom score; N-rTOSS = nighttime reflective total ocular symptom score; 24hr-rTOSS = average of D-rTOSS & N-rTOSS; iTOSS = instantaneous total ocular symptom score; INS = intranasal steroid spray; MCFB = mean change from baseline over entire treatment period; NRQLQ = nocturnal rhinoconjunctivitis quality of life questionnaire (16-items assessing 4 domains individually & globally (sleep problems, sleep time problems, symptoms on awaking in morning & practical problems); AM = morning (prior to taking dose); PM = evening; PNIF = peak nasal inspiratory flow; AEs = adverse events; HA = headache

Citation	Duration	Design	Treatment/ SS	Inclusion/ Exclusion Criteria	Endpoints	Results
Data on File[25]	2 week	MC, RDM, DB, PG, DD, PBO-controlled Conducted at 42 US sites (Aug 07 – Nov 07)	FFNS 110 mcg & oral PBO capsule QD (n=224) FEX 180 mg capsule & vehicle-PBO nasal spray QD (n=227) vehicle-PBO nasal spray & oral PBO capsule QD (n=229) Total SS: 680	**Inclusion:** • Age ≥12 years • Hx of SAR to ragweed with a ≥2 year diagnosis • (+) skin prick test to ragweed • Pts clinically symptomatic during screening period: NSS ≥4.5, congestion on awakening ≥2, D-rTNSS ≥6, reflective nasal congestion ≥2, D-rTOSS ≥4, & diary completion >80%. **Exclusion:**• Significant concomitant medical conditions, defined as but not limited to: Hx or current evidence of clinically significant uncontrolled disease of any body system; severe physical obstruction of the nose or nasal septal perforation; nasal or ocular injury/surgery within 3 months; asthma except mild intermittent; rhinitis medicamentosa; bacterial or viral infection of the eyes or upper respiratory tract within 2 weeks; acute or significant chronic sinusitis; current or hx of glaucoma	**Primary:** • MCFB in NSS **Key Secondary:**• MCFB in 24hr-rTNSS, D-rTNSS, N-rTNSS, pre-dose iTNSS • MCFB in 24hr-rTOSS, D-rTOSS, N-rTOSS, pre-dose iTOSS **Other Secondary:** • MCFB for NRQLQ • MCFB in AM & PM PNIF	**Results:** • FFNS significantly greater improvements in NSS, 24hr-rTNSS, D-rTNSS, N-rTNSS, & pre-dose iTNSS vs. FEX & vs. PBO (P <0.001) • FFNS significantly greater improvements in 24hr-rTOSS, D-rTOSS, N-rTOSS, & pre-dose iTOSS vs, FEX & vs. PBO (P≤0.034) • FFNS significantly greater improvements in NRQLQ (global score) vs. FEX & vs. PBO (P<0.001) • FFNS significantly greater improvements in AM & PM PNIF vs. FEX & vs. PBO (P<0.001) **Safety:** • AEs similar in nature & incidence for FFNS, FEX & PBO • Most common AEs for FFNS: HA (4%), pharyngolaryngeal pain (1%) • Most common AEs for FEX: HA (4%), epistaxis (2%), pharyngolaryngeal pain (1%) • Most common AEs for PBO: HA (3%), epistaxis (<1%), pharyngolaryngeal pain (<1%)

MC = Multi-center; RDM= randomized; DB = double-blind; PG = parallel-group; DD = double dummy; PBO = placebo; FFNS = fluticasone furoate nasal spray; QD = daily; FEX = fexofenadine; SS = study subjects; Hx = history; SAR = seasonal allergic rhinitis; pts = patients; NSS = nighttime symptom score (sum of scores for 3 questions relating to nasal congestion on awakening, nighttime awakenings due to nasal symptoms & degree of difficulty going to sleep due to nasal symptoms for a total score up to a maximum of 9); TNSS = total nasal symptom score (sum of scores for rhinorrhea, nasal congestion, nasal itching & sneezing for a total score up to a maximum of 12); D-rTNSS = daytime reflective total nasal symptom score; N-rTNSS = nighttime reflective total nasal symptom score; 24hr-rTNSS = average of D-rTNSS & N-rTNSS; iTNSS = instantaneous total nasal symptom score; TOSS = total ocular symptom score (sum of scores for itching/burning, tearing/watering, & redness for a total score up to a maximum of 9); D-rTOSS = daytime reflective total ocular symptom score; N-rTOSS = nighttime reflective total ocular symptom score; 24hr-rTOSS = average of D-rTOSS & N-rTOSS; iTOSS = instantaneous total ocular symptom score; INS = intranasal steroid spray; MCFB = mean change from baseline over entire treatment period; NRQLQ = nocturnal rhinoconjunctivitis quality of life questionnaire (16-items assessing 4 domains individually & globally (sleep problems, sleep time problems, symptoms on awaking in morning & practical problems); AM = morning (prior to taking dose); PM = evening; PNIF = peak nasal inspiratory flow; AEs = adverse events; HA = headache

Citation	Duration	Design	Treatment/ SS	Inclusion/ Exclusion Criteria	Endpoints	Results
				&/or cataracts or ocular herpes simplex; clinical evidence of a nasal *Candida* infection; hx of any psychiatric disorder or other conditions that would limit or confound interpretation of study results; hx of renal impairment, sleep disorders, or Hepatitis B or C • Systemic, inhaled, ocular, or topical corticosteroid within 8 weeks • INS within 4 weeks • Use of other allergy medications within a specified timeframe • Use of other medications that affect the study medications, allergic rhinitis or its symptoms		

MC = Multi-center; RDM= randomized; DB = double-blind; PG = parallel-group; DD = double dummy; PBO = placebo; FFNS = fluticasone furoate nasal spray; QD = daily; FEX = fexofenadine; SS = study subjects; Hx = history; SAR = seasonal allergic rhinitis; pts = patients; NSS = nighttime symptom score (sum of scores for 3 questions relating to nasal congestion on awakening, nighttime awakenings due to nasal symptoms & degree of difficulty going to sleep due to nasal symptoms for a total score up to a maximum of 9); TNSS = total nasal symptom score (sum of scores for rhinorrhea, nasal congestion, nasal itching & sneezing for a total score up to a maximum of 12); D-rTNSS = daytime reflective total nasal symptom score; N-rTNSS = nighttime reflective total nasal symptom score; 24hr-rTNSS = average of D-rTNSS & N-rTNSS; iTNSS = instantaneous total nasal symptom score; TOSS = total ocular symptom score (sum of scores for itching/burning, tearing/watering, & redness for a total score up to a maximum of 9); D-rTOSS = daytime reflective total ocular symptom score; N-rTOSS = nighttime reflective total ocular symptom score; 24hr-rTOSS = average of D-rTOSS & N-rTOSS; iTOSS = instantaneous total ocular symptom score; INS = intranasal steroid spray; MCFB = mean change from baseline over entire treatment period; NRQLQ = nocturnal rhinoconjunctivitis quality of life questionnaire (16-items assessing 4 domains individually & globally (sleep problems, sleep time problems, symptoms on awaking in morning & practical problems); AM = morning (prior to taking dose); PM = evening; PNIF = peak nasal inspiratory flow; AEs = adverse events; HA = headache